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Pseudomonas Aeruginosa Infections

By CLAUDE E FORKNER JR , M D

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Preface

SUPERINFECTIONS CAUSED BY antibiotic resistant bacteria are commonplace. With the advent of new drugs which alter the balance of bacterial flora, and with the development of new therapeutic measures such as organ transplantation and chemotherapy of cancer requiring the suppression of natural body defense mechanisms, the threat of resistant infections has become paramount.

Infections due to *Pseudomonas aeruginosa* in their severe form are sufficiently uncommon that many physicians do not have wide experience in their diagnosis and management. Many important contributions have dealt with single case reports or isolated experiences; many others are available only in foreign journals and foreign languages. It is with these issues in mind that the present comprehensive review of pseudomonas infections was undertaken.

The author's personal experience has been limited for the most part to those infections developing in the setting of malignant disease; however, it is evident that many of the lessons learned will be applicable whatever the underlying disease process will be. A report of clinical experience with septicemia due to *Pseudomonas aeruginosa* has previously been published.[140]

The clinical data have been presented so that different systems of the body are dealt with separately. Within each section, insofar as possible, reports have been discussed chronologically. It is hoped that this will represent the most effective way of presenting the available information.

Many hundreds of references were scanned in compiling the present bibliography. The references included are believed to be representative, pertinent, and up to date.

The author wishes to express his deep appreciation to Dr. C. Gordon Zubrod, Clinical Director, National Cancer Institute, Bethesda, Maryland, for his encouragement and constructive criticism. A particular debt of gratitude is owed to Dr. John Edgcomb, Department of Pathology, National Institutes of Health, Bethesda, Maryland, who had the major responsibility for the section

To Kate

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CLAUDE E FORKNER JR M D

1 *Characteristics of Pseudomonas Aeruginosa*

BACTERIOLOGY

Pseudomonas aeruginosa (B pyocyaneus Ps pyocyanea B aeruginosum) is a lender rod shaped actively motile flagellated gram negative bacterium with rounded ends Its stated dimen ions are 1 5 to 3 0 micra in length and 0 5 micron in breadth Frequently it grows in short chains of two or more organi m The number and position of flagellae may vary within a given strain[17] The organism is aerobic and does not form spore It forms acid from glucose but from no other sugar[3 0 8 39] Growth occurs at temperatures rang ing from 5 to 42 C The optimal growth temperature is 37 C[417] The bacteria grow in large spreading colonie which may vary morpho logically Gelatinous variants exi t[83 378]

Classification of strains under the genus P eudomonas i difficult because of their variety and wide range of activity Criteria for their separate identification are unsettled *Ps aeruginosa* is the only member of the genus known to be pathogenic for humans A labora tory test for the identification of *Ps aeruginosa* based on the high intracellular concentration of cytochrome oxida e and the forma tion of indophenol blue has been de cribed[1 4] Cood review of bacteriologic tudies of *Ps aeruginosa* are available[1 15 1 4 193]

ENDOTOXINS

Filtrates of broth cultures of pseudomonas have demonstrated proteolytic activity[11 46] Likewise potent endotoxins have been identified Piromen (formerly Pyromen) is a purified cell free prod uct obtained from pseudomonas[3] which has been u ed in fever therapy[33] and in the study of pyrogenic reactions In 1950 Bennett

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and Beeson [3] published a comprehensive review of pyrogen. The most potent known pyrogens appear to be those associated with the somatic antigens of gram negative bacteria.[331, 461, 464]

The physiologic disturbances produced by endotoxins were reviewed in 1954 by Thomas[413] and a syndrome of vascular collapse was described.[4 4] Several clinical and experimental reports pertain to the mechanism of this state.[31, 41, 11, 1 0, 183] Experimentally no qualitative difference in action or effect has yet been found between the endotoxin of *Ps aeruginosa* and that of other *gram negative* bacteria. Progressive illness and eventual death occurs in some patients whose blood has been rendered sterile by antimicrobial agents. This is in accord with the concept that the pathologic effects of pseudomonas infection are not so much those of living bacteria as of their toxic products. One endotoxin of gram negative bacteria consists of phospholipid and polysaccharide moities sometimes associated with protein or polypeptide.[464, 464] Landy [63] has demonstrated that removal of protein from such a complex does not alter the biologic characteristics of the endotoxin.

PIGMENTS

The best known pigment of *Ps aeruginosa* is pyocyanin, a deep blue phenazine derivative,[45] soluble in both chloroform and water.[41] It was first isolated from cultures of pseudomonas in 1860 by Fordos.[13] The relatively innocuous effect of pyocyanin on human skin and leukocytes has been investigated.[8] Pyocyanin constitute a reversible oxidation reduction system and acts as a respiratory catalyst. It has been termed the major respiratory enzyme of *Ps aeruginosa*.[3 4] Pyocyanin formation is specifically inhibited by certain respiratory poisons (KCN) which suggests that respiratory enzymes are involved in pyocyanin biosynthesis.[181] Other pigments may be formed.[417] Many strains lose the ability to form pigment apparently irreversibly [153] and *many original isolates are non pig*mented.[1, 163, 167, 8]

Bacterial fluorescence of *Ps aeruginosa* has been reported.[274] This characteristic has been used clinically [88] as well as in the identi

fication of cultures Chromatographic investigations have been de scribed by Rivera cited by Williams[4 ,] who thought that ubcla sifi cation of strains on the basis of pigment formation ultimately might be u eful

ANTIBIOTIC ACTIVITY

Substances with antibiotic activity have been i olated from ex tracts of *Ps aeruginosa*[4 115 1 136 3] Methods for the production purification and i olation of ome of the e have been de cribed[1,6 413 414] These antibiotics have been variously attributed to enzymes pigments and endotoxins Activity again t typhoid fever[4 3] diph theria[1] *F coli*[4 9] *M tuberculosis*[16] viru e[19] fungi[3 134] and gram positive bacteria have at one time or another been described

SEROLOGY AND IMMUNITY

P eudomonas infection induces production of agglutinin A titre higher than 1 30 is rarely encountered in a normal per on but titres of 1 1000 or higher may occur during systemic infection[19] Neter and Weintraub[3 7] sugge t u e of the conditioned bacterial hemagglutination test to differentiate actual infection from carrier state This test eems to offer greater ensitivity than the conven tional bacterial agglutination te t it depends on the ready adsorp tion of the somatic antigens of *Ps aeruginosa* by erythrocytes which are then pecifically agglutinated by homologous bacterial anti bodies Gaines and Landy[1 6] have demonstrated in random human era the presence of *Ps aeruginosa* hemagglutinins in the ab ence of bacterial agglutinins this sugge ts that man mu t come in contact with and develop an immunologic response to *Ps aeruginosa* more frequently than is generally appreciated

EPIDEMIOLOGY

Ps aeruginosa i widely di tributed in nature The percentage of people who are carriers of p eudomona in the inte tinal tract has been variously estimated from 0 04 to 15 5 per cent[83- 1 9 1 9] Studies on the epidemiologic feature of p eudomonas infec

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EPIDEMIOLOGY

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tion are available[170, 86, 7, 358] Recent observations emphasize the adaptability of pseudomonas organisms to all kinds of liquid media including antiseptic solutions[6a, 6b, 86, 345] as well as urine bottles and bed pans[30] Transmission may occur by way of contaminated hands of ward personnel[30] since infections are largely confined to hospitalized patients Revealing studies on the prevention of

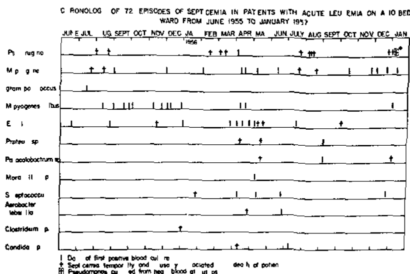


FIG 1 — Illu tration of grouping of generalized P eudomona infections in con tra t to more random di tribution of other infection on a leukemia war l (From Forkner et al P eudomonas epticemia Am J Me l 25 877 1958 Reprinte l by permi ion of the publi her)

Ps aeruginosa infections in irradiated mice and rats have been re ported[444] Widespread infection originated from carriers and was propagated by fecal contamination of drinking devices Elimination of the e cau es controlled the epidemic In our own experience pseudomonas septicemia has occurred in several small epidemics in patients with acute leukemia treated on the same ward[140] Thi was in contrast to the more random temporal distribution of other infections as indicated graphically in FIGURE 1 Epidemics have been noted el ewhere[315, 319]

PATHOGENICITY

In 1850 Sedillot demonstrated the transferability of greenish blue discolorations on surgical dressings[3,4] Lucke in 1862[93] showed that this condition was infectious and saw rod shaped elements in the discharge In 1882 Gessard[163] obtained *Ps aeruginosa* in pure culture from two cutaneous wound discolored blue green Gruber[184] in 1887 recovered *Ps aeruginosa* from green suppurations of the ear Despite early demonstration by Charrin[6] in 1889 of pathogenicity for animals recognition of the pathogenicity of this organism for man was not immediate

In regard to *Ps aeruginosa* Ford quotes Schimmelbusch[37] While it can cause local inflammation and general symptoms it never invades the body at least in adults Osler[334] in reference to *Ps aeruginosa* wrote Although this is not a frequent cause of septicemia and pyemia it nevertheless deserves special mention It is probably not an independent pathogen but occurs only as a secondary invader in existing lesions—especially of the mouth and skin As shall be illustrated given the proper predisposing circumstances there is scarcely a region of the body exempt from infection with *Ps aeruginosa*

2 *Clinical Manifestations of Infection*

SEPTICEMIA

Since Finkelstein[119] in 1896 first reported blood cultures positive for *Ps. aeruginosa* it has become firmly established that this organism may produce septicemia. Although Finkelstein is generally credited with the first ante-mortem report of pseudomonas septicemia, Williams and Cameron[448] in 1893 and 1894 observed two children with typical courses; post-mortem cultures were positive for pseudomonas from the internal organs in one and from the heart blood in the other. They termed the disease cyanopyaemia. Their observations were not printed until 1896 because of a delay in transit to the publisher. These writers in turn credited Ehlers[113] in 1890 with isolation (post mortem) of pseudomonas from the blood and organs of similar cases. As a result of systematic bacteriologic study of 800 consecutive autopsies at the Johns Hopkins Hospital, Barker[1] in 1897 was able to find 11 cases of either local or general pyocyanic infection. A severe hemorrhagic tendency and a high incidence of smooth muscle paralysis were noted in these cases.

The pathogenicity of pseudomonas for animals had already been noted.[4] In his treatise, La Maladie Pyocyanique, Charrin presented a summary of the pathogenicity of pseudomonas in rabbits.[63] The pathogenicity of pseudomonas in dogs was described by Cadéac[5] in 1890.

Lartigau[6] in 1898 reported three cases of pseudomonas infection in man and described the clinical evolution of maladie pyocyanique. Characteristic features of septicemias were reported to be irregular fever, vasomotor disturbances, focal necroses, and hemorrhagic lesions in the parenchyma of viscera with a predilection for the small bowel. A high incidence in children was noted. The following year Brill and Libman[40] reviewed the literature and

reported the first adult patient with pseudomonas septicemia Pigmented spots were noted over the body the possible relationship of these to circulating toxic factors was considered

In 1901 Wassermann[4] reported an epidemic of 11 newborn infants with umbilical infections terminating in fatal pseudomonas septicemias Most of these patients had pulmonary disease Babes[13] also recorded a case of pseudomonas septicemia which originated in the umbilicus

Waite[4] in 190[illegible] reviewed the literature and added two cases Fraenkel[144, 147] in four monographs written between 1906 and 1925 discussed at length and in great detail the histopathologic changes associated with generalized pseudomonas infection In particular he described the characteristic appearance of pseudomonas lesions in the skin and blood vessels which is said to be pathognomonic of infection by this organism To quote directly The anatomic basis for all the organic changes of pyocyaneus infection is to be sought in a characteristic typical colonization of the bacilli in the walls of the blood vessels in the diseased foci and in the locally induced disturbance in nutrition increased by toxic influence This finding even without the cultural identification of the bacilli permits of an anatomic diagnosis of pyocyaneus infection Examples of this feature are shown in FIGURES 2 and 3

Dold[104, 106] in 1918 and 1919 reported a relationship of pseudomonas infection to a typhoid like fever locally known as Shanghai fever or 13 day fever These illnesses were associated with splenomegaly and a roseola like maculopapular skin exanthem they resembled typhoid or paratyphoid fever in their clinical picture and course Usually in the absence of complications patients became afebrile in two or three weeks Pseudomonas was isolated from the blood urine feces and skin repeated attempts to isolate or agglutinate typhoid or paratyphoid organisms were unsuccessful Lilley and Bearup[79] in 1928 described 9 patients with generalized pseudomonas infection originally thought to be typhoid fever The organism was cultured from the blood in 2 (possibly 4) of the 9 cases The authors were also impressed by leukocytosis as a differentiating diagnostic feature distinct from typhoid fever The viru

2



3

FIG 2—*(abote)* P eudomona vasculiti ubmucosal connecti e ti ue m uth Hematoxylin-eo in (× 1100)

FIG 3—*(b low) Ps a rugin sa* in and near the wall of cap llaries ul utane u a lipose ti ue al d men H matoxyl n-eo in. (× 1?00)

lence of the bacteria was considered to be increased by passage from patient to patient.

Epstein and Grossman[119] in 1933 emphasized the potential virulence of pseudomonas *in children, particularly in infants, as compared* to adults. They reported a 7 year old child with a history of abscesses in the axillary and anogenital regions who had an 18-day course of fever and rectal pain associated with icterus, splenomegaly, purpura, thrombocytopenia, leukopenia, agranulocytosis, rapidly spreading infection, and death. Ante mortem cultures of the blood and stool were positive for pseudomonas. At autopsy the characteristic gross and microscopic lesions of pseudomonas infection were found throughout the body. Examination of the tibial marrow revealed many fat cells, absence of myeloid cells, and very few megakaryocytes.

Stanley[404] in 1947 reviewed the literature and reported 5 cases with terminal septicemia. One of these had bacterial endocarditis. Kerby[36] reviewed 83 reported cases of pseudomonas septicemia. Of 39 cases in children, the apparent portal of entry was the gastrointestinal tract in 25.7 per cent, the skin in 15.4 per cent, and the middle ear in 12.6 per cent. In 44 cases of infection in adults, septicemia occurred after operative procedures in 31.9 per cent—most commonly after urologic procedures.

Keefer and Hewitt[33] as part of a program designed to evaluate the therapeutic effectiveness of streptomycin collected by 1948 a series of 3,000 infections treated in the United States. Of these there were 19 patients with pseudomonas septicemia. The portals of entry were the urinary tract in 8 cases, skin wounds in 4 cases, the upper respiratory tract in 1 case. In 5 cases the primary focus was unknown. There were 10 deaths, a fatality rate of 53 per cent.

Mirabel[31] in 1952 over a period of 11 months collected 18 cases of septicemia due to pseudomonas from the pediatric department of San Juan City Hospital. With the exception of one 10 year old child, all patients were younger than 16 months. Diarrhea was the original complaint in 61 per cent of the cases, and in these the gastrointestinal tract was assumed to be the portal of entry. Other apparent sources were otitis media 11 per cent, umbilical cord 5.5

2



FIG 2—*(abo e)* P eudomona va culiti ubmuco al connective ti ue mouth Hematoxylin eo in (× 1100)

FIG 3—*(belo v)* *Ps aeruginosa* in and near the walls of capillaries ubcutaneou adipo e ti ue al do nen Hematoxylin eo in (× 1500)

accounted for approximately one half 12 patients had septicemia due to *Ps aeruginosa* 6 p eudomonas infections were thought to have originated from the genito urinary tract (5 following cys to copy) 1 from the skin and 5 from unknown foci All had fever and 8 had chills Two had metastatic ab cesses Thrombocytopenia occurred in 2 cases and agranulocytosis in 1 of the e Of the 12 patients 2 had ecthymatous lesions None of 3 patients who received polymyxin B died however 1 patient who received only tetracycline died

During the years 1954 through 1956 23 cases of epticemia due to *Ps aeruginosa* occurred at the Clinical Center of the National Institutes of Health The great majority of the e patients had acute leukemia Of the 23 cases 22 were fatal and all of the e were autopsied Ob ervations on this eries with illustrations of the more important clinical and pathologic features have been reported[140]

GRANULOCYTOPENIA AND THROMBOCYTOPENIA

Brill and Libman[46] in 1899 reported 2 ca es of p eudomonas septicemia and remarked on the ab ence of leukocytosis despite a fulminating infection Gheroghiew ky[1 8] the same year claimed to have found a leukocyte de troying ferment in cultures of p eu domonas In 1906 Rolly[3 3] among other early writers stressed the pre ence of hemorrhagic diatheses and abnormal coagulability of the blood in the e infections Freeman[148] in 1916 postulated a leucocidin as re ponsible for the leukopenia Hirszfeld et al[94] in 1948 de cribed 14 infants with pseudomonas infection 9 of whom died The authors were frequently able to culture pseudomonas from aspirated tibial or femoral marrow when blood cultures were negative They associated granulocytopenia and thrombocytopenia with involvement of the bone marrow Lovett[8] found that injec tions of p eudomonas could reduce the leukocyte count of guinea pigs and cau e degeneration of leukocytes in the peritoneal cavity Linthicum[91] in 1927 Dasse[90] in 1928 and Delatour[98] in 1932 injected pseudomonas into animals intravenously and observed that the bacterium or its products apparently caused granulocytopenia by destroying granulocytes or by inhibiting their formation

M1616

per cent post operative or post instrumental 5 5 per cent unknown 11 per cent Symptoms and signs in order of frequency were fever 83 4 per cent diarrhea vomiting skin lesions cyanosis edema jaundice (16 6 per cent) hepatomegaly and splenomegaly Agranulocytosis and thrombocytopenia were not observed The over all mortality was 67 per cent Polymyxin B was not used

Martin and co workers[98] in 1954 reported 10 cases of septicemia due to *Ps aeruginosa* encountered at the Mayo Clinic over a period of 13 years All the patients had fever usually of a high spiking type and 7 of the 10 had chills One patient had thrombocytopenia and developed necrotic lesions on the buttock Another had a large erythematous lesion of the thigh leukopenia thrombocytopenia and jaundice The portal of entry was the genito urinary tract in 7 cases Of the patients 3 who had serious associated conditions died Polymyxin B was not used

Hoffman and Finberg[07] suggest that a very humid environment contributed to the increasing incidence of pseudomonas infections noted in their nursery Of 13 infants with pseudomonas infection 3 developed septicemia and died and 2 others with local infections died Only 3 of the 13 had received antibiotics prior to infection All were treated with polymyxin B

Koch[243] in 1956 reported studies on 50 instances of septicemia due to gram negative bacteria of the opportunist pathogen group occurring since 1951 All the patients were men and all had received some form of chemotherapy prior to the onset of septicemia Six patients with pseudomonas septicemia died One patient infected by both *E coli* and *Ps aeruginosa* and treated with tetracycline survived Portals of entry in the 6 cases were urinary tract 3 intestinal tract 1 respiratory tract 1 skin 1 All of the pseudomonas septicemias were of sudden onset and five were preceded by instrumentation

Spittel and co workers[403] in 1956 reviewed all cases of bacteremia due to gram negative bacteria exclusive of cases of typhoid fever brucellosis and bacterial endocarditis that were treated at the Mayo Clinic between 1940 and 1954 * Of 137 cases collected *E coli*

* This series included patients reported earlier by Martin et al [illegible]

accounted for approximately one half 12 patients had septicemia due to *Ps aeruginosa* 6 pseudomonas infections were thought to have originated from the genito urinary tract (5 following cystoscopy) 1 from the skin and 5 from unknown foci All had fever and 8 had chill Two had metastatic abscesses Thrombocytopenia occurred in 2 cases and agranulocytosis in 1 of these Of the 12 patients 2 had ecthymatous lesion None of 3 patients who received polymyxin B died however 1 patient who received only tetracycline died

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M1616

More recently Hubbard and co workers [14] have described experiments wherein a strain of pseudomonas recovered from the intestinal tract of an infant was introduced into mice and rabbits and produced the characteristic necrotic lesions They also noted preferential disintegration of granulocytes when blood cells were exposed in vitro to a mixture of pseudomonas and proteus organisms They postulate a capacity of pseudomonas to inactivate leukocyte proteolytic enzymes in order to explain the coagulative type of necrosis produced by these organisms Markley and co workers [9] recently studied pseudomonas septicemia in Peruvian patients with burns and found that although the leukocyte count was usually in the normal range if the course was rapidly fatal there was leukopenia or if the course was prolonged before death there was leukocytosis

Many other reports have dealt with the relationship of agranulocytosis to infection with *Ps aeruginosa* [1 58 90 98 150 34 41 49 70 81 83 91 31 3 9 3 3 379 380 39]

BACTERIAL ENDOCARDITIS

Bacterial endocarditis is a rare manifestation of infection with *Ps aeruginosa* At least 20 cases have been reported Some information about these cases is recorded in Table 1 In some instances the diagnoses appear certain in other cases (5 6 12 14 17) diagnoses seem uncertain In at least 11 patients the mitral valve was involved

TABLE 1—*Reported Cases of Endocarditis Due to Ps Aeruginosa*

Author	*Patient*	*Valve*	*Remarks*
Barker [15] (Thayer) [4 1]	41 F	Mitral	Portal probably intestinal tract Pseudomonas cultured from mitral vegetation ovaries bowel
Blum [35]	2[1] mo M	Mitral	Congenital syphilis Focus of infection unknown Pseudomonas obtained in pure culture from vegetations
De la Camp [9]	51 F	Mitral	Skin probably portal of entry Blood culture negative prior to death Pseudomonas cultured from heart blood and mitral valve

Another possible case was not translated up to the time of publication [4 6]

TABLE 1—Continu d

Author	Patient	Val e	Remarks
Rolly[2]	28 F	Mitral	Bowel probably portal of entry Pseudomonas recovered from spinal fluid and blood before and after death Also cul tu ed from vegetations
Bun eler	65 M	M tral	Patient had RHD with mitral in uf fi ency T eated with Sapr t n (h in P eudomonas) There was en loc rd ti of mitral val e w th perf ration No pos tive blood culture obtai ed Vege tation not cultured
K a	35 M	Aortic M tr l	Port l of entry skin ab ce P eudo monas cultured from blood and ur n b fo e death. Not cultured after death Had typical h tolo c chan s of ndo card ti Bacteria in aorta and pulmonary art ry
Fi h et al [33]	?1 M	Aortic	Pseudomonas septicemia—prob bly f om ur nary tract Gram n gati e rods in alve veg tat ons Ki lneys and aorta in lved.
M r ue an l Ander on	66 M	M tral	P eu lomonas septicem n diabetic with RHD Port l probably urin ry t act Had m t al steno i Pseudomo as cultured f om veget t ons
St nley	45 M	Tr c pid	P eud monas sept cemia follow g Pneu mococcus XII epticem a Pseudomon s cult r d from val e Treated w th sulfa pen llin and a tipneum o cus erum
DeM th and Raw n	40 M	Aort c	Pseud mon sept c m a from int t nal t a t Treated w th strept my n and pyo yaneu ph
H ll [20]	28 F	Tric p id	Hi tory of heumat c fe er age 8 Pu per l P eudom nas septic mi Acut bact al endocarditis at necropsy Treat d w th pen c lli t eptomycin p lymy
B [3]	19 F	No proof	Au cult t ry e de ly P e domona in spi l flui l f llow n ab t n No d mo trated ept emia

TABLE 1—*Continued*

Author	*I atient*	*I alve*	*Remarks*
Coller and Dyer[78]	53 F	Aortic Mitral	Lung probably primary site No previous known valve damage P eudomonas cultured from blood urine feces and throat before death Smears and cultures of vegetations positive Multiple antibiotics
Kenoyer et al[235]	20 M	No proof	History of RHD since a e 7 with valvular damage P eudomona epti cemia Recoverd with neomycin
Wal lren and Ha tings[431]	81 M	Mitral	Hi tory of RHD Blood cultures po itive before and after death Smears and cultures of vegetation po itive for P eu domonas Treated with multiple anti biotics
Brund on et al [9]	37 F	Mitral	Remittent fever 1 week after mitral comi urotomy with P eudomona in blood and putum Died 9 weeks after valvulotomy P eu lomonas cultured f om lung ab ce s bone marrow valve vegeta tion
Gott egen and Romoda[1]	18 M	No proof	Four year cour e of endocarditis with hi tory of polyarthriti and defective heart valve P eudomonas cultured from blood and urine during last 6 month Cured by plenectomy after re i tant to all tried antibiotic
Curtin et al [7]	26 F	Aortic	No h tory of RHD or known previou murmur Developed fever chills 4 blood cultures were po itive fo P eudomonas *Developed A V fi tula after operation for* ectopic pregnancy which probably be came infected at time of cysto copy 2 months prior to death
McDonald et al[3 1]	23 M	Aortic Mitral Tricu pid	Narcotic addict with recu rent rheumat c fever Blood cultures po tive before and after death Culture of vegetation po i ti e for P eudomonas Multiple ant b otics

TABLE 1—*Conti d*

Author	*Pati t I /*	*Rema ks*
Te tel and Fl rman[4]	14 F	Pat ent was febrile 20 weeks after co rective su gery for p t nt ductus and in teratrial septal defect R current fe er ch ll pl nome aly a d many blood cul t r s po iti e fo p eudomona I ter mitte t pos t blood cultures de p te pr longed antibiotic admi trat on in *clud ng high do age of p lymyxin B* Re operation di clo d a 2[1] cm ilk suture dangli in the right atr m r rou de l by c l n s of *Ps aeruginosa* Following exci ion of this po t perati e cour e was be n a d the p t ent re cov red

in 3 of these there was as ociated involvement of the aortic valve The aortic valve alone was affected in 3 ca es and the tricu pid valve alone in 2 others Positive blood cultures were never obtained in 2 of the less certain ca es Liedberg mentioned without detail the occurrence of acute endocarditis in 4 burned patients whose ante mortem blood cultures were po itive for p eudomonas In 3 of these patients at lea t one other organi m was cultured from the blood

CUTANEOUS LESIONS

Many and varied descriptions of cutaneous lesions attributed to pseudomonas appear in the literature among which are the follow ing petechiae[111] ro eola like[104 106] maculopapular[14] infiltrative[7] hypertrophic[409] simulating lepro y[9] ery ipelas like cellulitis[3] erythema multiforme like[41] erythema nodosum[47] exfoliative[186] pellagra like[10] hemorrhagic[360] vesicular[347] bullous[113] multiple ecthymata[3 8] pemphigold[107 347] pustular[343] ulcerative[131] gangren ous[1 471] necrotic[98] Some of this apparent variation may be attributed to the natural morphologic evolution of the lesion in its various tages of maturity

Lesions beginning as macules or ve icle later becoming bullous

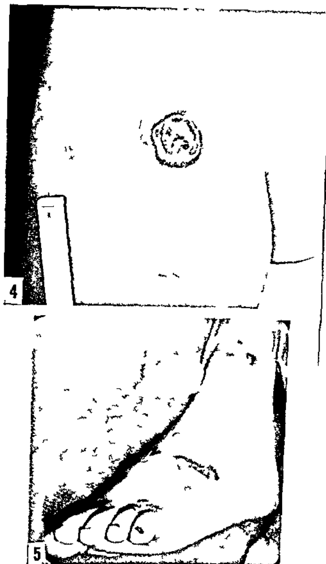


Fig 4—*(above)* Characteri tic appeara ce of ecthyma gang enosum Note the black coagulative necrotic center and umbil cated margin Inflammatory react on i m nimal

Fig 5—*(below)* Characteri tic appearance of P udomona cellul ti esicular form One esicle has ruptured and i a suming an umbilicated ecthymatou ap rearance (From Forkner et al P eudomona septicem a Am J Med 25 8 7 19 8 Reprinted by permission of the publi her)



6

FIG (—E t e necrotic l erated al ce e i lvin the buttocks and back of th s 13 year ld g l with acute yel ytic le k mia Th b ear hemor h c thoracic l on i h rj zo t r *l s ae ugino a* a l otl r e i tant o ganı m were cult ed from th l tto ks l ions

or pustular and eventually loughing to form gangrenous ulcers already ob erved by Ehlers [113] and others were described by Bar ker [1] in 1897 and considered by him to be cutaneou manifestations of systemic pseudomonas infections Hitschman and Kreibich [0] the ame year gave to the e lesions the name of ecthyma gangren osum Robin on [361] referred to the dermatologic manifestations of p eudomonas epticemia as Characteri tic and consisting of profuse cutaneous hemorrhages that tend to suppurate and become gangrenous—preceded by initial vesicles that develop in petechiae and purpuric macules Ecthyma like cru ted areas are the result of this morphologic change

Ecthyma gangr o um A pu tul erupti u lly se ted o ε ha dened ba e nd e ircl d by an flammatory area The pu t l s d harg lea g spot f p gm ted c c t at on [1 7]

A typical cutaneous lesion starts as an erythematous macule often in the ano genital area which rapidly becomes vesicular containing a cloudy opalescent fluid from which the organism may be cultured. The lesion may exist singly or in clusters. The surrounding tissue is inflamed and tender. Following rupture a circular hard dark crusty core develops. This is characteristically surrounded by a narrow rim of erythema. There is little or no evidence of inflammation peripherally and the lesion is non tender. The histologic changes are similar to those of pseudomonas lesions elsewhere in the body. Variations in the form of flattened hemorrhagic well demarcated areas of cellulitis may occur. The vesicular stage may be absent. Illustrative lesions are shown in FIGURES 1–6.

In our own series of patients the onset of septicemia in a few cases was preceded or accompanied by the appearance of pink round or oval maculopapular plaques on the trunk measuring up to two centimeters in diameter. These were evanescent and their relationship to systemic infection or to the previously described cutaneous lesions uncertain. Seeding of the blood stream from cutaneous lesions is probably common and the reverse process occurs in some cases.

Bauer and Cohen [19] have described with colored illustrations 4 cases of infection of fingernail with *Ps aeruginosa* as the primary offender. *Candida albicans* was also present in 3 of these. They found the most effective treatment to be 0.1 per cent polymyxin B sulfate in 1 per cent acetic acid followed by 2 per cent methylrosaniline. Other reports of infected fingernails are available [175, 310]. Howe [14] described invasive infection of the leg due to pseudomonas; this was successfully treated with surgical debridement and topical 10 per cent urethane solution.

BURNS

With the advent of antibiotics a reduction in the incidence of gram positive bacterial contamination of burns was achieved. However no comparable effect has been noted for burns contaminated with *Ps aeruginosa*. Jackson et al [1] in 1951 (at the Burn Re

earch Unit of the Birmingham Accident Hospital found that in burned patients pseudomonas were responsible for more fatal chest complications and septicemia than any other organism. The local application of 0.1 per cent polymyxin significantly reduced the incidence of contamination of burns with pseudomonas and promoted the healing of graft. Other studies[75,73] have shown that secondary infection with pseudomonas tend to occur on the wards rather than prior to admission or on an outpatient basis and that infected burns or wounds were the major sources of pseudomonas on the ward.[7]

Markley and coworkers during the course of study of burns in Peru encountered a high incidence of fatal septicemias due to *Ps aeruginosa* clinically manifested by cutaneous lesions which generally preceded death by from 1 to 12 days. These cutaneous lesions involving burn free areas were of two types. The first and more common of these was a vesicle which became necrotic and was followed by the appearance of many similar lesions over the body. This type was noted in 72 per cent of children with cutaneous lesions. Generally death occurred from 24 to 48 hours following the appearance of the first vesicle. The second type of lesion was nodular and subcutaneous occurring in 26 per cent of patients with cutaneous lesion. Generally it was followed by death in from 2 to 12 days. The burns at this stage were covered by bluish green pus or by a black crusted eschar. *Ps aeruginosa* could be cultured from such areas. An unusual feature of this study was the very high incidence of pseudomonas septicemia in this hospital (29 of 172 burned children developed characteristic cutaneous lesions and of the 25 who were cultured 22 had septicemia due to *Ps aeruginosa*). The incidence of septicemia in adults was less. No effective therapy was found although antibiotics including polymyxin were administered in the usual dosages.

MENINGITIS

Meningitis due to *Ps aeruginosa* is uncommon. Neal[3,3] in 1935 reviewed 3178 cases of meningitis occurring in New York between

1910 and 1924 she found only 4 attributed to pseudomonas Tripoli in 1936[41] at Charity Hospital New Orleans reviewed 468 cases of bacterial meningitis from 1925 to 1934 Of these 4 were due to pseudomonas and 3 were fatal Barron[16] in 1918 reviewed the literature and found 39 cases of meningitis in infants under 3 months of age Of 19 reported in the newborn only 1 of them was caused by pseudomonas Pastor and coworkers found only one meningeal infection from pseudomonas at the Philadelphia General Hospital between 1939 and 1949 More recently Smith collected a series of 409 patients with purulent meningitis at the Children

TABLE 2 —*Cumulative Data on Recorded Cases of Pseudomonas Meningitis*

Author and date	*Total*		*Primary*		*Secondary*		*Unknown*
	No	*Mortality (per cent)*	*No*	*Mortality (per cent)*	*No*	*Mortality (per cent)*	*No*
Evans 1936	39	67	17	47	18	83	4
Kernan 1943	56	58	29	45	21	85	6
Stanley 1947	71	68	41	55	30	86	0
Forkner 1957	230	40	144	39	74	66	12

Data through 1955

Hospital in Los Angeles Bacteria were isolated from 316 cases and only 5 of these were pseudomonas Of the 5 patients 3 died[394] Nevertheless pseudomonas is possibly the most common cause of bacterial meningitis following lumbar puncture

Ehlers in 1890 first reported meningitis due to *Ps aeruginosa* however the cerebrospinal fluid was not cultured[113] Kossell[48] in 1893 described the first proved case an infant whose source of infection was otitis media and from whose pia and heart blood pseudomonas was recovered in pure culture after death In 1936 Evans[1 3] reviewed the literature and collected 39 cases of which 29 were fatal (see TABLE 2) She considered 18 of her cases to be secondary to generalized infection and reported a mortality of 83 per cent In 1943 Kerman et al[37] assembled 55 cases from the literature and added one of their own which had occurred following pneumoencephalography A wash bottle used in the procedure was

found to be the source of contamination Of the 56 ca e 21 were econdary to epticemia with a mortality of 85 per cent The over all mortality from pseudomonas meningitis found by Stanley in 1947 in a review of 71 ca es was 68 per cent Of 41 primary ca es the mortality was 55 per cent of 30 econdary ca es the mortality was 86 per cent The increa ing number of reported ca es (primary and econdary) is illu trated in FIGURE 7

PSEUDOMONAS MENINGITIS

Cumulative Bar Graph of Reported Cases Through 1955

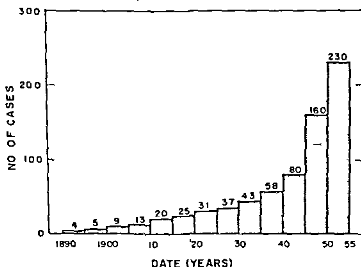


FIG 7—Th graph llu t ates the n e sing numbe of po t d ca s of me ngit d e to *Ps a gi osa* du i the la t decade

Reported ca es of p eudomonas meningitis have u ually been classified as either *primary* or *secondary* in origin Unfortunately the meaning of these term ha been ubject to individual inter pretation o that stati tical evaluation of cumulative series becomes very difficult Primary i here defined to mean direct introduction of the bacteria into the central nervous sy tem econdary hall refer to hematogenou meningitis Situations involving pos ible

direct extension of infection such as otitis media [48] or mastoiditis [3 9] with subsequent meningitis have been classified according to the clinical features of the case in question

Schlagenhaufer [373] is usually credited with describing the first case of primary pseudomonas meningitis In 1911 he reported 5 cases developing after spinal anesthesia The source of contamination was a saline solution Three of the patients died Chauffard and Laroche [6] in 1917 reported a case following the intrathecal administration of tetanus antitoxin Other cases have been reported following wound of the head [1 41 56] spinal wounds [4] infected spina bifida [169] pneumoencephalography [0 3] myelography with Pantopaque [06] laminectomy [6] burr holes [6] radical mastoidectomy [27] meningeal ureteral anastamosis for hydrocephalu [343] excision or rupture of meningomyelocoele [233 36] and exploration for brain tumor [418] The most common preceding event however is lumbar puncture as a diagnostic [1 3 4 3] ane thetic [3 3] or therapeutic [6 193] procedure A chronologic listing of reported primary cases is available in TABLE 3

TABLE 3 —Primary Meningitis

Authors	Year	A e Group	Cases	Outcome		Remarks
				Died	Recovered	
Schlagenhaufer [373]	1911	A	5	3	2	Spinal ane the ia (contaminated sal ne)
Chauffard and Laroche [67]	191	A	1		1	I T† tetanus antitoxin following football njury
Abadie and Laroche	1918	A	1		1	Head wound Therapy own serum inje ted I T

Patients 15 year and ove are l te l as adult below 15 year ch ldren and 1 year and under infants

† Intrathecal

Lumbar puncture

§ Intramu cular

¶ Intravenous

* Streptokina e—Strep todorna e

TABLE 3—Continued

Authors	Year	Age Group	Cases	Outcome: Died	Outcome: Recovered	Remarks
Sonnensche n [0]	1923	A	1	1		L.P.+
S hn ider[3 5]	19[illegible]4	A	1		1	Spinal anesthesia used [illegible] argochrome and ar [illegible]flamin
Levy and Cohn	192[illegible]	A	1		1	L.P. I.T. inactivated autogenous blood serum spinal drainage
V ll et al	1928	A	1		1	Spinal gunshot wound. Therapy autogenous vaccines
Va ban et al	1931	A	1		1	? L.P. or septicemia from tonsillitis
Ghon[160]	1932	I	1	1		Infected spina bifida
Shrewsbury	1934	A	1		1	Spinal anesthesia. Therapy repeated spinal drainage
Bh tn ar	1934	A	1	1		Spinal anesthesia
E n F L.	1936	A	3	2	1	L.P.
Ibrahim	1937		1		1	L.P.
Berg	1938		1		1	L.P. I.T. inactivated autogenous blood serum
Iwa ake and Mot na	1939		1			Pneumoencephalography
W se and M er	1939		6	2	4	L.P. (contaminated mercury manometer). Therapy Sulfa and repeated spinal drainage
K man et al [37]	1943	C	1	1		Pneumoencephalography (with bottle contaminated). Therapy Sulf
Botterell and M n [4]	194[illegible]	A	11	9	2	Penetrating head wound (2 from contaminated penicillin). Therapy Penicillin and sulfa
E an F T	194[illegible]	A	2	2		Spinal anesthesia (? head wound) contaminated distilled water

TABLE 3—*Continued*

Authors	*Year*	*Age Group*	*Cases*	*Outcome* Died	Recovered	*R marks*
Kremer [54]	1945	A	4	1	3	2 spinal anesthesia 2 contaminated penicillin
Decourt et al [96]	1945	A	1		1	Spinal ane thesia Th rapy Sulfadiazine
Pulaski and Mathews[348]	1946	A	1		1	Stm i m § i v ¶ and i t
Cairns et al [56]	1946	A	3	3		Brain ab ce s from gun hot wounds — Therapy Stm i t and in ventricle
Harris et al [193]	1946	2A 2I	4	1 1	1 1	Contaminated penicillin u ed to treat menin-oco cal menin-itis Therapy Penicillin sulfa draina
Cawthorne [6]	1946		2			Spinal anesthesia
David on [91]	1947	A	2	1	1	Spinal anesthesia Therapy Sulfa
Merwarth et al [307]	1947	A	1		1	Spinal anesthesia Theraj y I enicillin sulfa
Medicolegal [303 304]	1947	A	4	3	1	Spinal ane thesia
Paine et al [336]	1947	C I I		 1	1 1	1 L I 2 spinal sur ery 3 ero ion of menin-ocele Therapy Penicillin sulfa treptomycin
Vuyl teke [8]	194	A	4	3	1	Spinal anesthe ia Therapy Sulfa
Keefer and Hewitt [33]	1948		9			7 related to L.P 2 from cervical meningocele
Lewin and Vollum [77]	1948	A	2		2	Head wound Tl apy Sulfa and streptomycin
Lewin [6]	1948	A	3	3		Head wounds
Weinstein [441]	1948	A	3		3	Spinal ane thesia Therapy Sulfa penicillin and str pto mycin

TABLE 3 – *Continued*

Auth rs	*Year*	*Age Grou*	*Ca s*	Outcome *D e l*	 *Re ver l*	*R marks*
S loenl ack	1949		3			*Infe ted h d woun l Th r* ap ı lymy in B t
Ra lke an l Cu n n ham ı	1949	C	1		1	Theraı v f m llin, lfa an l treıt my n
Germer an l K app[16]	1949	A	1	1		I P Th raı y tr ptomyc n
T llett 5	1949	A	1		1	Hea l woun l — 7 month ur-e — finally cured with SK SD
B esgen 3	1949	A	1	1		Spı al ne th ıa Theraı y l enı ll n a l lfa
Neter et al[3 8]	19 0	C	1		1	Lam ne tomy Theraı y Sulf an l chl rtet acycl ne
G mes et al[177]	1950	A	1		1	Therapy Int a pinal penic l h a d treptomycin — re l pse — r peat d with o l ulfa (no focu)
Hayes a l Yow 94	1950	A	1		1	Sp nal nesthes a fo appen dectomy polymy in B ı t a l m
Debre et al.[93]	19 0	I	3	3		1 Ventrı lar pu ture for hydr eı halu 2 Antrotomy for ot Therapy st epto my n a l penicill n
Se l ll on et al 8	1951	A	1		1	Spı l ne the ıa — 6 re l pse — Therapy tra *tricular trept myc n*
Reıtter[355]	1951	A	1		1	Spı l an the The py Sulfa
Pedell an l Paley[2]	19 1	A	1		1	Th apeut c LP Th py Sulf a d streptomycin
B usq a d Brygoo[5]	1951	I	1	1		Probably L P (was be ng tre ted for p eumo occ l mening t)

TABLE 3—*Continued*

Authors	*Year*	*Age Group*	*Cases*	*Outcome* Died	*Outcome* Recovered	*Remarks*
De baillets[1]	19 1	A	1		1	Spinal anesthesia Therapy streptomycin
Pastor et al[337]	1951	2A	2		2	Spinal anesthesia Therapy i t streptomycin
Jawetz[6]	1952	C	2		2	1 Following burr hole 2 Residual hydrocephalus Therapy polymyxin i t
Ginsberg and Hyman[1]	1952	A	1		1	Following radical mastoidectomy — streptomycin and chlortetracycline
Kreitner[3]	1952	A	1		1	Spinal anesthesia Therapy Sulfa and streptomycin—4 relapses
Schmeiser[3]	1952	C	3	1	2	Following diagnostic L.P s chloramphenicol i t and p o
Ditkowski et al[3]	1952	I	1		1	Following operation on meningocele Therapy neomycin i m
Knight et al[4]	1952	A	1		1	Following laminectomy Therapy SK-SD and neomycin i m and i t
Troen and Dicaprio[40]	1952	A	1		1	Spinal anesthesia Therapy Oxytetracyclin
Yow[60]	1952		3			No detail
Douha et al[109]	1952	A C I	3	3		Operations for meningocele and hydrocephalus
Cutler and Cutler[85]	1953	2A	2		2	Spinal anesthesia Therapy Chloramphenicol and oxytetracycline in one and streptomycin in the other
Reitter[3]	1953	A	1		1	Spinal anesthesia for hysterectomy

TABLE 3—*Continue l*

A tl o	*Year*	*Ag Cro l*	*Cases*	*Outcome* *Die l*	*R cover l*	*Remarks*
Monnet an l I u t Merm t [4]	1) 3		1			D gnostic and th rapeutic I P
Piette [3 5]	1953	I	1	1		*Following men ngo ureteral* ana t mosi for hydroceph alus Th rapy polymy in—3 relapses
Sm th C E C [3]	1953	A	1		1	Following LP for skull fract re Therapy Chlo mphenicol
F r ell [4]	1954	C	1		1	Follow „ explo ation fo ependymol la toma Ther apy polymyxin L
B hl and H mbu ger [9]	1954	A	5	3	2	Follow g CNS procedures (3 spinal anesthe ias 1 men oc le 1 spinal treatment The apy polymyxin B
Lo ell Sm th [8]	1954	C	1		1	Following mpound frac ture n al fo or LP Ther py Polymyxin B i t
Blum g	1954	I	1	1		Follow g ruptu e of my lo-cystocele
Mabille et al.[2]	19 5	A	1	1		I m th aft bull t hea l inj ry Th rapy polymyx n B t. and i m
Frey chmidt [1 9]	1955	A	1		1	Spinal ane thesi
E g t dt a d Olhagen	195	A	1		1	Spinal ane thes a Therapy oxyt t acycl ne i a d poly myx i m a d i t
Bo din et l.[43]	1955	A	1	1		LP (pn umoencephalo-gram) Therapy streptomy in nd polymyxin
Stoj ic an l Vojvo lic	1955		1			

Meningeal infection in secondary cases is the result of hematogenous spread from a focus elsewhere in the body. This may be *from localized abscesses*[6] *stomatitis*[240] *enteritis*[60] *or following* ureteral instrumentation[41c] The pathway in infants is often via the umbilicus. Meningitis may occur following *in utero* infection[340] or circumcision. Reported cases of secondary pseudomonas meningitis are chronologically listed in TABLE 4.

TABLE 4—*Secondary Meningitis*

Authors	*Year*	*Age Group*	*Cases*	*Outcome* Died	*Outcome* Recovered	*Remarks*
Ehler [113]	1890	C C	2	1	1	Both had typhoid like septicemia (brother and sister) Spinal fluid not cultured
Kossel [48]	1894	I	1	1		Otitis media (pure culture of Pseudomonas from pia and heart blood)
Pesina and Honl [341]	1894	A	1	1		Primary site unknown
Councilman et al [81]	1898		1			Mixed with *Staphylococcus aureus*
Perkins [340]	1901	A	1	1		Abortion followed by septicemia (*P*seudomonas in CSF * and liver)
Berka [2]	1903	A	1	1		? Pneumonia Pure cultures from purulent meningeal foci
Horder [11]	1904	A	1	1		Chronic otitis media
Rolly [363]	1906	A	1	1		Abortion followed by septicemia (mitral valve involved)
Hubener [215]	1907	A	1	1		Pelvic abscess opened—led to septicemia and meningitis
Benfey	1907	I	1	1		Infection of umbilicus
La niffoul et al [2 9]	1910		1	1		Typhoid like septicemia

* Cerebrospinal fluid

TABLE 4—*Continued*

Authors	Year	Age Group	Cases	Outcome: Died	Outcome: Recovered	Remarks
F ae kel	1912	A	1	1		Sept cem a—no ob ou fo cu
Gaeth en	1914		1	1		T b rcul us m n n itis
Frae kel [6]	191	I	1	1		*Ch o uc ot t m ha*
Ca elli	1919	I	1	1		Enterit s epticem a
Dud len [109]	1922	C	1	1		Sept emia (f om ddle ear)
Neal	1 4	C	1			
Khew and Koch	1924	C	1		1	St matiti
Ch ari [68]	1926	I	3	3		Probably umb l u —P eu d mona in meninge and I ricard un
Gau h aud and Pi e d [8]	1928	I	1	1		Infection of mbili us (? fr m amniot c fluid)—(hy d o ephal s)
Le d ham	1930	A	1	1		N obvi u focu
Baum ter [0]	1931	A	1		1	No obvio foc
Be i	1933	C	1	1		Sept cem a otit s m d a
Meyer nd P elin	1935		1		1	O b tal b ce f o u f ei n l dy
N eh	19 6	C	1	1		M stoid t
R l t a d B l ey	1937	A	1		1	Tul rculo empyem witl ec dary fe t i
Slut ky a d M thn	1939	A	1	1		S pticem a w th focu in r ght k d ey—treated with l ter pha
All	1941	I	1	1		Infect n of umbil c (mother ha l eve P u d n o a enter ti)
Kr u and Hu t	1941	I	1	1		Prol al ly umb l us

Meningeal infection in secondary cases is the result of hematogenous spread from a focus elsewhere in the body. This may be from localized abscesses[*] stomatitis[240] enteritis[60] or following ureteral instrumentation[416] The pathway in infants is often via the umbilicus. Meningitis may occur following *in utero* infection[340] or circumcision. Reported cases of secondary pseudomonas meningitis are chronologically listed in TABLE 4.

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Kossel[218]	1894	I	1	1		Otitis media (pure culture of Pseudomonas from pia and heart blood)
Pesina and Honl[341]	1894	A	1	1		Primary site unknown
Councilman et al[8]	1898		1			Mixed with *Staphylococcus aureus*
Perkins[340]	1901	A	1	1		Abortion followed by septicemia (Pseudomonas in CSF and liver)
Berka[25]	1903	A	1	1		? Pneumonia Pure cultures from purulent meningeal foci
Horder[211]	1904	A	1	1		Chronic otitis media
Rolly[363]	1906	A	1	1		Abortion followed by septicemia (mitral valve involved)
Hubener[15]	1907	A	1	1		Pelvic abscess opened—led to septicemia and meningitis
Benfey	1907	I	1	1		Infection of umbilicu
Lagnifoul et al[2 9]	1910		1	1		Typhoid like septicemia

* Cerebrospinal fluid

TABLE 4—Co t ued

Authors	Y ar	Age Group	Cases	Outcom: Died	Outcom: Recovered	Rema ks
Fr enkel [44]	1917	A	1	1		S pticemia—no ob ious fo c
Caethgen	1914		1	1		Tubercul us m ningiti
Fraenkel [146]	1917	I	1	1		Chron c ot t m lia
Can lli	1919	I	1	1		Ent iti septicemia
D dden [0]	19.2	C	1	1		Septicem (from mi ille ear)
Neal	1921	C	1			
Kliew a l K ch	1924	C	1		1	Stom t t
Ch ari [65]	19??	I	3	3		Pr bably uml il c +—I eu lomona n menin s a l pe ca dium
Gau h raud and Pi d [19]	1928	I	1	1		Infection f uml l u (from amn otic fl ii)—(hy d ocephalu)
Le d h m [265]	1930	A	1	1		N ob iou foc
Baume ter	1931	A	1		1	No ob ious foc
Bert	1933	C	1	1		Sept mia ot ti media
M yer nd R el ng	193		1		1	Orl tal al ce from f ei n body
N h	1936	C	1	1		M t diti
R l n a l I elsey	1937	A	1		1	Tul rc lou emj yema w th eco dary infe ti n
Slut ky and Matl	193?	A	1	1		Sept em a with fo u in ght ki l ey—tre t d w th b ter pha
Allin	1911	I	1	1		Infecti n of u ib l cu (moth r had se e P eu l m n s enteriti)
Krau a l Hunt r	1941	I	1	1		Pr l lly uml il s

Table 4 — Continued

Authors	*Year*	*4 e Group*	*Cases*	*Outcome* *Died*	*Recovered*	*Remarks*
Moragues and Anderson [18]	1943	A	1	1		Infection of urinary tract
A ulnik	1946	I	1	1		Circum i ion Treated with ulfa penicillin and spinal drainage
Stanley [434]	194	C	1	1		Septicemia treated with treptomycin
Keefer and Hewitt [33]	1948		2			Secondary to epticemia
Schaffer and Oppenheimer [30]	1948	I	2	2		Septicemia from appendix
Hirzfeld et al [4]	1948	I	2	2		Therapy L P Therapy Sul fathiazol
Viklicky [40]	1948		1	1		Hepatic ab es or cy tit s
Debre and Mozziconacci [94]	1949	I	4	3	1	Septicemia from inte tinal tract—Therapy streptomy cin i m and i t
Appelbaum et al	1949		4	2	2	Introduced during i t peni cillin for pneumococcal men ingitis
Zimmermann [46]	1949		4	4		2 lo e gastro nte tinal and 2 rhinopharyngitis — Ther apy penicilli sulfa and treptomycin
Glanzmann [14]	1950	C	1		1	Unknown focu Therapy i t pen c ll n and strepto mycin
Lodenkamper and Schiersmann [8]	1950	A	3		3	2 after encephalo raphy 1 after suboccipital puncture Treated with autovaccine sulfonamides spinal tap Blood transfu ion 1 had con ale cent serum i t

TABLE 4—Co t ued

				Outc me		
A th s	Year	Age Group	Ca es	D ed	Pecover d	Remarks
l)one	19ɔ0	A	1		1	Follow: ≈ al ortı n (LP not excl d d) The apy trej to ycin an d ulf
Fa eka and N kod mu z	19 0	C	1		1	Foc s inte tın l t act Therapy pen cıllin strepto mycın ı t
Co co et l	19 0	I	1		1	Sept c m a (GI t a t) Therapy pen c llın trep t myc n
Toml n [6]	19 1	A	1		1	Septicem a followin u te r l n t un entat o —Ther apy polymy n B ı t
L u ı d Brv o	19 1	I	1		1	Umbilicus
C n ber nd Hyman	19ɔ?					
Weihe	19 2	C	1		1	B l t al ma to d t tr at d w th streptomycın after peni ıll n f led
An J et l	195	I	1	1		Hemato enou from ab es
D uha t al	1952	I	1	1		Sept c m a (? f om th gh ab c)
L nzan o and Mold	1953	C	1		1	Lap tomy fo appendec tomy ? te tın l t act Ther apy polymyxın B (? LP)
Peter et al	19ɔ3	C	1		1	Oc urr d 1 mo th aft pe fo ated append Th apy o ytetracycl ne ı v and ı t
Ma a l D tt rı	19 3	I	1		1	? Hem to enou (LP n t excl ded) Ther py poly myx n B

TABLE 4 —*Continued*

Authors	Y ar	A.e Group	*Cases*	Outcome Died	Recovered	*Remarl s*
Moragues and Anderson [18]	1943	A	1	1		Infection of urinary tra t
Agulnik [2]	1946	I	1	1		Circumcision Treated with sulfa penicillin and pinal draina e
Stanley [4 4]	194	(	1	1		Septicemia treated with treptomycin
Keefer and Hewitt [33]	1948		2			S condary to epticemia
S haffer and Oppenheimer [3]	1948	I	2	2		Septicemia from appendix
Hirzfeld et al [204]	1948	I	2	2		Therapy L I Therapy Sul fathiazol
Viklicky [4 6]	1948		1	1		Hepatic ab ces or cystitis
Debre and Mozziconacci [4]	1949	I	4	3	1	S pticemia from intest nal tract—Therapy strep tomy cin i m an i t
Appelbaum et al [5]	1949		4	2	2	Intro luc l durin i t peni cillin for pneumococcal m n ingitis
Zimmermann [46]	1949		4	4		2 l wer ga trointe tinal and 2 rhinopharyngitis — Ther apy penicillin ulfa and trep tomycin
Glanzmann [7]	1950	C	1		1	Unknown focu Therapy i t penicillin an l strepto mycin
Lodenkamper and Schier mann [8]	19 0	A	3		3	2 after encephalo raphy 1 after ub occipital puncture Treated with autovaccine ulfonamides spinal taps Bloo l tran fu ion 1 had con ale cent rum i t

Information derived from sensitivity studies on bacterial cultures is often of critical importance in prescribing therapy Levaditi [35] reported the identification of *Ps aeruginosa* cultures by using ultraviolet light to demonstrate the fluorescent greenish yellow pigment This technic has been used in the diagnostic evaluation of spinal fluid [85]

The characteristic relapsing course of pseudomonas meningitis may be explained by the anatomic changes in the central nervous system Fibrin may be deposited in the subarachnoid space the infected cerebrospinal fluid may be loculated by adhesions These collections resistant to therapy may remain for long periods of time before releasing their contents into the circulating spinal fluid Kremer [4] reports that so long as the condition is confined mainly to the spinal canal the arachnoiditis is not likely to cause serious complication however if infection involves the brain adhesion may obstruct the flow of cerebrospinal fluid causing hydrocephalus He attributed rigidity of the back to irritation of spinal roots from fibrinopurulent cuffing of the nerve roots

At necropsy the brain in pseudomonas meningitis is covered to some extent by a greenish yellow exudate Typical histologic finding of the meninges are illustrated in FIGURE [9]

Prior to the discovery of sulfonamides pseudomonas meningitis was treated by spinal drainage [38] or by autogenous vaccine administered intrathecally [4] In general the results of therapy were poor however some patients recovered [3 4] Penicillin and sulfonamides had no apparent effect on the mortality statistics Harris and co workers [193] in 1946 reviewed the results of the use of sulfonamides and penicillin in this disease and found that of 21 patients treated with these drugs 15 (72 per cent) died For several years case reports of many writers attest to the popularity of streptomycin [5 3 8 77 311 337 401 441] Weinstein and Perrin summarized four recoveries among nine patients treated with streptomycin [441] At that time although certain disadvantage were apparent a combination of sulfonamides and streptomycin was considered the therapy of choice Intrathecal injection of streptomycin was frequently associated with an increased number of cells in the cerebrospinal fluid and exces

TABLE 4—*Continued*

Authors	*Year*	*Age Group*	*Cases*	*Outcome*		*Remarks*
				Died	*Recovered*	
Heinecker[198]	1953	C	1		1	Unknown focus—treated with chlortetracycline and frequent L P s—air introduced
Widerman[445]	1953	I	1	1		Upper respiratory infection—died 12 hours after admission
Chi_ter[0]	1953	I	1	1		Intestinal tract (? L P) Therapy chloramphenicol sulfa and penicillin
Jansen[2 5]	1954	I	1	1		Therapy chlortetracycline polymyxin B and streptomycin i m and i t
Hoffman[208]	1954	I	1	1		? Congenital infection
Smith R T[395]	1955	I	1		1	Septicemia oxytetracycline and chloramphenicol
Jone R F M	1955	\	1		1	Chronic otorrh a and suppurative otiti med a Therapy polymyxin B i t and i m

Clinical sign of pseudomonas meningitis usually appear within 24 to 48 hours after seeding but may be delayed The onset is rapid with nuchal rigidity and a high spiking fever Polymorphonuclear leukocytosis is common in the spinal fluid Characteristically the spinal fluid i cloudy and contains increased albumin and fibrin and decreased sugar Commonly few or no bacteria are een on smears of the spin il fluid The di ease may either terminate rapidly with cure or re ult in rapid death of the patient Frequently how ever a chronic indolent apparently low grade infection will super vene which is resistant to many or all antibiotic agent Apparent cure is o ten followed anywhere from days to month by relap e which may recur many time in the ab ence of appropriate therapy

sively large individual doses were known to have caused serious reactions[36, 376]

Tillet[41] in 1949 described the successful use of enzymes in the treatment of meningitis due to pseudomonas SK SD (15 000 units streptokinase and 3750 units of streptodornase) was injected intrathecally at two day interval In one patient meningitis which had been refractory to treatment with sulfonamide chlortetracycline chloramphenicol and streptomycin for seven months responded quickly The issue is confused however since *intrathecal* and intramuscular neomycin was given concurrently Knight et al in 1952 also reported the successful use of intrathecal SK SD in conjunction with neomycin in a case of pseudomonas meningitis which had followed laminectomy

Occasional favorable reports followed the use of chlortetracycline[2, 6] oxytetracycline combined oxytetracycline and chloramphenicol and chloramphenicol alone A combination of chlortetracycline and streptomycin was used successfully[17] in one case

A number of factors may in part be responsible for the increase in number of reported cases during the last few years (FIGURE 7) Among these are the advent of antibiotics with the tendency to report only successful therapy the increasing number of medical authors and journals and an increasing awareness of and interest in *the disease The more frequent use of lumbar puncture for spinal* anesthesia as well for other diagnostic and therapeutic procedures is not the only factor since the incidence of secondary as well as primary meningitis has increased

Through the year 1955 at least 230 cases of pseudomonas meningitis have been referred to in the literature about 60 per cent of these are considered primary The remaining cases are considered *secondary to a septic focus elsewhere in the body Of the 111 pri*mary cases 39 per cent were fatal of the 74 secondary cases 66 per cent were fatal The over all mortality rate is 46 per cent This information is illustrated in TABLE 2 Although the incidence of meningitis would appear to be increasing the mortality for both primary and secondary cases is decreasing

At the Clinical Center 6 cases of meningitis secondary to pseu

Fig. 8.—(*above*) Hemorrhages and thrombi. Pseudomonas meningitis.

Fig. 9.—(*below*) Pulmonary abscess. Possible portal of entry. Bronchiectasis, chronic. Acute thrombotic vasculitis, large pulmonary vessel.

Pneumothorax suddenly occurred and empyema developed On drainage of the pleural space pseudomonas was cultured from the exudate Sterility of the lesions and clinical cure followed repeated *blood transfusions and local and intramuscular therapy with peni*cillin and streptomycin In a series of 37 patients with pseudomonas infection Yow[469] listed 5 with parenchymal pulmonary infection *and 4 others with empyema All these cases developed during or* following treatment with antibiotics Firket and Doulra[131] described 4 adults with pseudomonas infection in the pleural cavity In only *one of these was there no previous history of instrumentation* through the pleura Other cases have been reported[73, 1 9, 145, 33]

Bronchopneumonia has frequently been reported[1, 3, 109, 1 1, 33, 41, 43, 3, 93, 313, 330, 381, 398, 4 4, 438] *A case from our own files is that* of H K with chronic lymphocytic leukemia who had received irradiation and who was being treated with adrenal cortical steroid *compounds She developed a chronic productive cough accom*panied by fever and chills *Ps aeruginosa* was cultured from the nose throat sputum and urine On x ray an infiltrate was seen in *the right upper lobe For two months her cough persisted as did* the pseudomonas in her sputum She received intensive treatment with penicillin streptomycin sulfonamides and polymyxin B She *developed anasarca and pleural effusions became disoriented and* died The necropsy findings included septic thrombosis of a pulmonary artery and vein in the lower lobe of the left lung septic *thrombi and emboli and infarcts in the brain thyroid gland heart* lungs and kidneys (FIGURE 9)

There have been several reports of fibrocystic disease of the pancreas associated with pseudomonas infection of the lung Garrard et al[1 3] observed 4 consecutive patients with pancreatic fibrosis in whom pseudomonas was the predominant organism demonstrable in the respiratory tract All had received prolonged antimicrobial therapy One had suppurative bronchitis and bronchiectasis with multiple pulmonary abscesses from which pseudomonas was grown in pure culture Another had suppurative bronchitis with purulent *viscid secretions forming a cast of the bronchial tree* from this pseudomonas was obtained in pure culture A third had acute and

domonas septicemia were diagnosed over a three year period from 1954 to 1957 All of these patients had leukemia Definitive diagnoses in most cases were made only at autopsy because of short survival times and overwhelming septicemia

RESPIRATORY INFECTION

Pulmonary lesions like cutaneous or meningeal lesions may be primary or secondary in origin and the evidence for one or the other is not always conclusive The respiratory tree seems seldom to be the portal of entry convincing reports of primary pulmonary infections are not common Meltzer [336] was able to produce broncho pneumonia in dogs by insufflation of suspension of *Ps aeruginosa* Once established respiratory infections with pseudomonas are often fatal [73, 109, 191, 330, 361, 398, 404] Infections in some patients may be prolonged and may respond to various forms of therapy [3, 86, 1, 181, 8] There is little doubt that the use of antibiotics has been a factor in the establishment of some of these infection [8, 301, 440, 460]

Pulmonary abscesses caused by pseudomonas may be single or multiple Robitzek [361] in 1946 reported a 5 month old infant with severe paroxysmal cough and fever for two months he became critically ill with cyanosis and dyspnea Treatment was instituted with sulfonamides and penicillin Numerous gram negative bacilli were seen in the sputum The pneumonitis spread to the right upper lobe and the infant died At autopsy the trachea and bronchi were filled with purulent mucus Numerous firm gray hemorrhagic patches 1 5 to 3 cm in diameter were in all lobes In the left upper lobe there was an irregular 5 by 7 cm cavity with a smooth gray membranous lining This contained gelatinous material from which *Ps aeruginosa* was cultured The authors considered this infection to have been of primary pulmonary origin

Pseudomonas empyema and pleuritis have been observed Glanzmann [1 4] in 1950 reported a 3 and one half month old infant with rhinopharyngitis and fever The abdomen became tender and distended and intussusception was suspected A bloody mucous enteritis developed and pseudomonas was cultured from the stool

old male by Raim in 1955[35] The patient was dyspneic had enlarged tonsils and rapidly developed stridor cyanosis and unconsciousness The epiglottis was large red edematous and contained a central elevated yellowish area which was open and draining Pseudomonas was cultured from this and uneventful recovery followed therapy with furadantin

GASTROENTERITIS

Lesions of the gastrointestinal tract due to *Ps aeruginosa* are similar in histologic appearance to those observed in other parts of the body they may arise from within the intestinal tract or by way of the blood stream Experimentally x irradiated mice are known to die with overwhelming spontaneous septicemia due to pseudomonas and other gram negative bacteria normally found in their intestines[31, 309] The feeding of broth cultures of organisms[1 0] or of mucin to irradiated mice increases the mortality A similar alteration of host bacteria relationship in man is suggested by the occurrence without evident portals of entry of septicemia due to pseudomonas and other intestinal flora in debilitated patients

There has been much speculation regarding the possible causative role of pseudomonas in epidemic diarrheas of the newborn The organism is found sufficiently often in the stools of asymptomatic persons to make evaluation of this difficult In adults pseudomonas enteritis has been confused with typhoid fever and is more frequently observed in the tropics[157] Bloody diarrhea[404] is the common initial and persistent symptom Fever vomiting dehydration skin rashes and jaundice are noted frequently

Epstein and Grossman[119] have reviewed the literature to 1933 mentioning the early cases and epidemics of enteric pseudomonas infection[14, 57, 79, 109, 1 1, 144, 147, 3), 64, 331, 43, 4] Ensign and Hunter[118] in 1946 reported an epidemic of diarrhea in 24 newborn infants in which there were nine deaths Of these infants 18 contracted the disease in a nursery All 9 infants who were studied bacteriologically had pseudomonas in their stools Symptoms in order of frequency were diarrhea vomiting dehydration cyanosis collapse pain and fever Treatment consisted of transfusions par

chronic bronchitis bronchiectasis and bronchopneumonia Other cases of this nature have been reported [86 108 131 133]

Infection with pseudomonas may be manifest as bronchitis O Brien [330] in 1950 described a 10 week old boy admitted with a productive cough his illness was diagnosed as pseudomonas tracheitis and bronchitis He died in eight weeks in spite of treatment with sulfonamides and penicillin At autopsy bronchitis and pneumonia were found *Ps aeruginosa* was obtained in pure culture One year later a sister of the first patient developed pertussis at 6 weeks of age The sputum was positive for *Ps aeruginosa* Treatment with sulfonamides penicillin streptomycin and polymyxin A was unsuccessful and she died at the age of 9 and one half months Other patients with bronchitis due to *Ps aeruginosa* have been reported [7 143 147 315 363] Pertussis like syndromes also have been noted [109 361]

Infection of the lungs due to *Ps aeruginosa* may give rise to asthma like symptoms which are a result of increased secretions edema and bronchospasm Jawetz [illegible] reported a 51 year old patient with a history of asthma who had received large doses of antibiotics A Caldwell Luc procedure had been done for relief of pseudomonas sinusitis The patient had purulent sputum post nasal drainage wheezes and rales in the lungs Cultures of the sinuses and sputum yielded predominantly *Ps aeruginosa* After a week of treatment with intramuscular polymyxin there was improvement in asthmatic symptoms sputum cultures became sterile Fein [1] reported a 7 year old girl who over a period of three months had received penicillin chlortetracycline oxytetracycline and streptomycin for bronchial asthma Because of continued wheezing and croupy cough the patient was admitted for bronchoscopy Pseudomonas was seen on smears of the bronchial aspirate and was grown in pure culture from the same specimen culture of the sputum had been negative Subsequent treatment with chloramphenicol and polymyxin B resulted in complete relief from asthma

Ulcers of the larynx trachea or other upper respiratory structures due to *Ps aeruginosa* have been reported [7 48 363] Acute epiglottic abscess due to pseudomonas was reported in a 12 year

enteral fluids penicillin sulfonamides and methylene blue The ource of contamination wa an infected rag which had been dripping into pa teurized milk at a dairy Schaffer and Oppenheimer [3 0] in 1948 reported infants with evere enteritis due to p eudomonas One patient had gangrenous appendicitis and another



FIG 12—Append x and c cum Acute append t due to P ae ugi osa

multiple perforations of the intestine Other complications included ileus dehydration acidosis leukopenia and hypoplasia of the bone marrow Only a single infant treated with streptomycin survived Walker [433] in 1952 reported 3 infants with diarrhea vomiting and fever all of whom had p eudomonas cultured from their stools Clinical improvement and negative tool cultures followed treatment with polymyxin B in 2 case The third patient died with septicemia cyano is and jaundice developed 18 hours after polymyxin was started Post mortem cultures of the stools were negative for pseudomonas

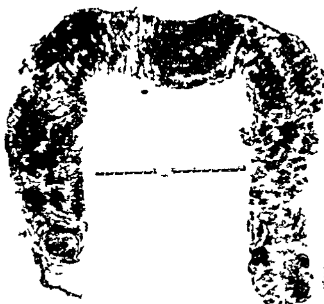




Fig 10—*(above)* E ten e ulcerati e and hemorrhagic colitis

Fig 11—*(below)* Gangrenou e oph gitis Mixed *Ca dida alb cans* and *Ps a ruginosa* infection

pital day At autopsy in the ileum cecum and colon were many small ulcers characterized by rolled borders undermined edges and little inflammatory reaction Gram negative rod shaped bacteria were found in abundance at the ulcer margins and pure cultures of pseudomonas were obtained from the lesion The wall of the ileum was greatly thickened gas bubbles were present between the mucosa and muscular wall The pathologic diagnosis was pneumatosis cystoides intestinalis Holgate [91] in 1954 described a 13 year old female who was hospitalized with fever diarrhea and abdominal pain Chloramphenicol was administered A rose spot slightly raised rash was noticed shortly before he lapsed into unconsciousness She was thought to have typhoid fever and died on the sixteenth day Blood cultures were negative but stool cultures contained a heavy growth of pseudomonas Mills and Kagan [310] gave oral polymyxin B to ambulatory symptomatic and asymptomatic individuals who were discovered to harbor pseudomonas in the intestinal tract Other related reports are available [31 6 74 85 104 138 1 187 14 79 311 4 5]

The incidence of gastrointestinal disease has been lower in our patients than in several other reported series However one patient had extensive ulcerative and hemorrhagic colitis (FIGURE 10) another had gangrenous esophagitis (Mixed *Candida albicans* and *Ps aeruginosa* FIGURE 11) A third patient had appendicitis caused by *Ps aeruginosa* (FIGURES 12 and 13)

GENITOURINARY TRACT

Data compiled from several sources [9 114 39] indicate that *Ps aeruginosa* is responsible for about 5 per cent of urinary tract infections Under certain conditions (a virulent resistant strain and a debilitated susceptible host) infection may rapidly lead to fatal septicemia Frequently however as in many cases of primary pseudomonas meningitis it is the physician who unwittingly introduces the infection by instrumental or operative maneuvers The catheter chill a phenomenon frequently noted after minor operative manipulation of the urinary tract has been associated with the introduc

Ceppert and co workers [161] cited the case of a 1 year old girl who was hospitalized with a history of diarrhea for two months She had been receiving penicillin for two weeks prior to admission Pseudomonas was the predominant organism cultured from her stools She was febrile dehydrated marasmic and died on the fourth hos



Fig 13 —Appendicitis due to *Ps aeruginosa*

emesis She was lethargic but there were no localizing neurologic signs The subsequent course is illustrated in FIGURE 14 *Ps aeruginosa* and *E coli* were cultured from the blood and urine Antibiotic were continued and blood cultures were negative after five days

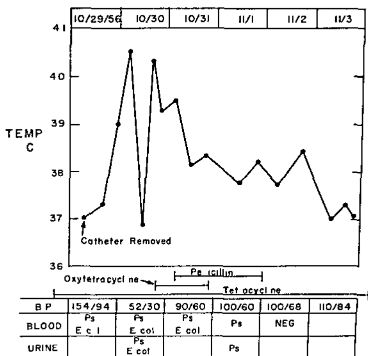
Waisbren[4] studied 29 patients with 31 bacteremias due to gram negative organisms 5 were due to pseudomonas and the genitourinary tract was considered the portal of entry in 4 of these Martin[98] in 1954 reported 10 cases of bacteremia due to *Ps aeruginosa* In 7 the portal of entry was the genitourinary tract In 5 of these an operative procedure on the genitourinary tract preceded the bacteremia Koch[43] reported 50 cases of bacteremia due to gram negative bacteria Over half the cases arose in the urinary tract The operative procedure most frequently followed by bacteremia was transurethral prostatic resection Of the 6 pseudomonas bacteremias 5 were preceded by instrumentation Of the six patients 3 died associated findings included cystopyelonephritis abscess of the kidney and pneumonia Spittel et al reported 12 cases of bacteremia due to *Ps aeruginosa* treated at the Mayo Clinic[403] Six of these originated in the genitourinary tract 5 after cystoscopy and 1 following ureterostomy In 5 the portal of entry was unknown

Although ascending infections are usually limited to the urinary bladder Stanley[434] reported a paraplegic debilitated 52 year old female who developed gangrenous cystopyelonephritis and died with pseudomonas septicemia Similar cases have been described [43] Reports of infection of the prostate and epididymis have been published [1, 133, 318, 371] Orchitis has been caused by pseudomonas [13, 3] Fatal meningitis due to *Ps aeruginosa* has followed circumcision complicated by infection

Keefer and Hewitt[3] in 1948 accumulated reports on 61 cases of acute infection of the urinary tract in which *Ps aeruginosa* was isolated as a single etiologic agent The primary clinical diagnoses were perinephritic abscess (2 cases) kidney abscess (1 case) acute cystitis (16 cases) pyonephrosis (2 cases) and acute infection of the urinary tract (28 cases) In 5 cases calculi were present 6 patients had a cord bladder and 12 patients had obstruction of the lower urinary tract In 7 per cent bacteremia was present prior

tion into the bloodstream of living bacteria. A small but significant proportion of these infections are caused by pseudomonas.

Of 23 reported cases of pseudomonas septicemia occurring at the Clinical Center,[140] the sole survivor was a 54 year old female (E. L.)



BP	154/94	52/30	90/60	100/60	100/68	110/84
BLOOD	Ps E. c. l	Ps E. coli	Ps E. coli	Ps	NEG	
URINE		Ps E. coli		Ps		

FIG. 14.—Febrile response to Pseudomonas septicemia following injury to lower urinary tract.

who was treated for carcinoma of the cervix by anterior pelvic exenteration and implantation of the ureters into an ileostomy. Her recovery was uneventful until three weeks after operation when *Ps. aeruginosa* was cultured from the ureter. One month later a ureteral catheter was removed with some bleeding from the ureteral mucosa. There followed in a few hours a sudden shaking chill and fever to 40.5 C. Her blood pressure dropped from normal ranges to 52 mm Hg systolic over 30 mm Hg diastolic. There was some bloody

eme i She wa lethargic but there were no localizing neurologic igns The ub equent cour e i illu trated in FIGURE 14 *Ps aeruginosa* and *F coli* were cultured from the blood and urine Antibiotics were continued and blood cultures were neg itive after five day

Wai bren [4] studied 29 patients with 31 bacteremia due to gram negative organisms 5 were due to p eudomona and the genitouri nary tract was con idered the portal of entry in 4 of the e Martin [?] in 1954 reported 10 cases of bacteremia due to *Ps aeruginosa* In 7 the portal of entry was the genitourinary tract In 5 of the e an operative procedure on the genitourinary tract preceded the bac teremia Koch [43] reported 50 ca es of bacteremia due to gram negative bacteria Over half the ca es aro e in the urinary tract The operative procedure most frequently followed by bacteremia was transurethral pro tatic resection Of the 6 pseudomona bac teremia 5 were preceded by instrumentation Of the six patients 3 died as ociated findings included cy topyelonephriti abscess of the kidney and pneumonia Spittel et al reported 12 cases of bac teremia due to *Ps aeruginosa* treated at the Mayo Clinic [43] Six of these originated in the genitourinary tract 5 after cv toscopy and 1 following uretero tomy In 5 the portal of entry was unknown

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to treatment Bacteriologic cure with streptomycin was obtained in 30 patients (49 per cent) Pseudomonas bacteremia was present in 3 of the 5 fatal cases and uremia was a feature in all fatal cases Pseudomonas was associated with *E coli* (14 cases) *A aerogenes* (9 cases), and various gram positive organisms (9 cases) Pseudomonas was the etiologic agent in 74 chronic urinary tract infections chronic cystitis (8 cases) subacute cystitis (2 cases), hydronephrosis (1 case) chronic pyelonephritis (25 cases), subacute pyelonephritis (11 cases) pyonephrosis (3 cases) chronic infection of the urinary tract (24 cases) Urinary calculi were present in 12 cases Bacteriologic cure was obtained with streptomycin in 31 patients (42 per cent) There was one death Pseudomonas was associated with gram negative organisms in 26 cases with gram positive organisms in 6 cases and with combined gram negative and gram positive organisms in 8 cases

Carroll and co workers[6] using streptomycin treated 39 patients



Fig 15 —Colony of *Ps aeruginosa* renal glomerulus Hematoxylin eosin (×400)

with infections of the urinary tract due to *Ps aeruginosa* and obtained satisfactory results in cases where in vitro testing demonstrated reasonable susceptibility Systemic toxic symptoms chills fever and frequency and urgency of urination were common Ulcers of the bladder were observed and large pieces of vesical membrane occasionally sloughed into the urine According to the authors pseudomonas organisms have the capacity to increase the alkalinity of the urine which may contribute to a sensation of burning on urination and lead to the formation of precipitates and encrustations Such encrustations may cover the bladder wall and partially or completely block indwelling catheters

As in the case of epidemic diarrheas pseudomonas may spread rapidly through a urological ward Pyrah and coworkers[314] described an outbreak in a ward devoted largely to the treatment of prostatism The epidemic was finally terminated by adopting a closed system of drainage of the bladder and by using better technic of sterilization

Histopathologic lesions of the kidneys have been noted in three of our patients FIGURE 15 shows a pseudomonas colony residing in a renal glomerulus This lesion presumably was the consequence of septicemia

PSEUDOMONAS INFECTIONS ASSOCIATED WITH PREGNANCY

In TABLE 5 are listed chronologically the reported cases of puerperal and/or congenital generalized infections due to *Ps aeruginosa*

TABLE 5 —*A Chronolog c Listin of Rep rted Case of P erpe l a d/o Co g nital Pse domo as I fect on*

Charrin[66] 1889	A ca e of puerperal infect on
Perkin 1901	2 ca age 21 and year The first ha l nfec t n follow ng s ptic a d in omplete abortion a d d l after a 7 w k ill es *P ae ginosa* was cul t red from uterine exudates a d from p nal flu d The second ha l ch ll and fever after d l ery and d d 6 week postpa tum w th purulent end metritis and lung ab ces e *Ps a rug osa* was cult red f m tle a ea

TABLE 5—*Continued*

Walthard[435] 1904	A 35 year old multipara with chills and fever 3 days postpartum. Pseudomonas was cultured from the lochia along with other organisms. The patient recovered.
Rolly[363] 1906	Following a septic and incomplete abortion Pseudomonas was cultured from the patient's blood and spinal fluid. She died on the 11th day. Pseudomonas was cultured from the heart valves and most of the body organs.
Delmotte[9] 1910	An 18 year old primipara was febrile 2 days after spontaneous delivery. Pseudomonas was cultured from the lochia but blood cultures were negative. The patient recovered.
Soifer 1928	A 34 year old multipara with pain, fever and chills following incomplete septic abortion was induced and the products of a 2 month gestation recovered. Pseudomonas was cultured from the blood and placenta. She recovered.
Caucheraud and Pigeaud[6] 1928	The mother had septic endometritis at delivery but recovered in 10 days. 4 days after delivery the infant developed meningitis and hydrocephalus. Pseudomonas was cultured from the ventricular aspirate and the infant died on the 34th day. (? contaminated spinal tap)
Allin[4] 1941	A 27 year old patient had fever, vomiting and diarrhea during delivery of a premature infant (34 weeks). Pseudomonas was cultured from the mother's stool. She recovered and was discharged after a 1 month illness. On the 5th day the infant developed red macular areas over the body and died with Pseudomonas meningitis.
Kraus and Hunter[5] 1941	The patient had enteritis the day before and chills during delivery. Stools were positive for Pseudomonas. The infant died 20 hours later with cyanosis, dyspnea, leukopenia and a macular rash. Cultures of the infant's blood, spleen, pleural exudate and brain exudate were positive for Pseudomonas.
Keefer and Hewitt[33] 1946	No clinical details. The patient [illegible]
Sobhi and Khairat[306] 1948	A 28 year old patient aborted in the 3rd month of gestation after a 2 day fever. Culture [illegible]

TABLE 5—Conti ue l

	urin stool an l cer ix were po ti e f r I eudo n ona Sl e d d 33 lays later Po tm rt m cultures from the per cardial flu l and lun s were po tive for P u lo nonas an l *E coli*
Hill 1949	A 28 year old primipara was induc d in the 7th month f p egnancy l ecau e of pre eclamptic tox emia She wa leliver d of a tillb rn female and a male who d ed in 4 hour P eudomona was *cultu d from the patient s l loo l urine and cervix* a d he di l after a 4 month illne with P u l mo as septicemia
N cora and S nna 195?	A 29 year ld primipara had diarrhea for 1 m nth pri r to abort on at 5 month gestation Sl di l o the 37th ho pital d y havin ha l ectl yma all over her l o ly P ud monas was ultur d from the loch am iot c flui l k n le ion mo th ulcera ti n pleu al flui l na al exu late an l fece The infant appeared normal l ut di l 2 h ur fter birth w th nten ely c n t d l i e an l pleen P e d mo as wa reco r l from th infant s l ver pleen bone marrow and m conium
Hoff r n 1954	A mal twin nfant wa edematou dy pnei and cyanotic and d ed 5 days after b rth I eu lom na w s cultured from th pleural exudate The nfant l o had menin ti an l myoca dit Th m ther wa well
Ko 1 1955	The m ther ha l nephr t aft r the 6th month of p e na cy A full t rm mal i fant lied on tl 4th d y w tl dy pnea cyano is and sk n macule P eu lomona wa ultur d from th infant s m lile ear li er gall bladder and pl u a
Stough d Shinner 1956	2 *ases* A 38 year ld multipa a bad chill and f er for days and al ort d a 3 i ch fetus Her blood cultu e wa po ti f r I eu lo non but *she mproved and eco e ed The fetus w not* infected A 2? y a old multigrav la was delivere l of a st llborn mal at 36 we k ge tation Sh had back ache n u a vo n ting hill and fe er H r bl od and stools were po it ve f r P udom na whi h wa al o g own from the bl d lung nd pl en of the infa t

TABLE 5—*Continued*

Walthard[435] 1904	A 35 year old multipara with chills and fever 3 days po tpartum P eudomonas was cultured from the lochia along with other organism The patient re covered
Rolly[363] 1906	Following a eptic and incomplete abortion Pseudo monas was cultured from the pati nt s blood and spinal fluid She died on the 11th day P eudomona was cultured from the heart valve and mo t of the body organ
Delmotte 1910	An 18 year old primipara was febril 2 days after spontaneou delivery P eudomonas wa cultured from th lochia but blood cultures were negati e The patient recovered
Soifer[39] 1928	A 34 year old multipara with pain fever and chill following incomplete septic abortion wa induced and the products of a 2 month ge tation recovered P eudomonas wa cultured from th bl d and placenta She recovered
Gaucheraud and Pigeaud[1] 1928	The mother had eptic endometriti at delivery but recovered in 10 days 4 days after delivery the in fant developed meningiti and hydrocephalu P eu domona was cultured from the ventricular a pirate and the infant die l on the 37th lay (? contaminated spinal tap)
Allin[4] 1941	A 27 year old patient had fever vomiting and diarrhea during delivery of a premature infant (34 weeks) P eudomona wa cultu ed from the moth er tool She reco ered and was di char ed aft r a 1 month illne s On the 5th day the infant de eloped red macular area over the body and d ed with Pseu lomonas m ningiti
Kran and Hunter 1941	The pat ent l ad enteritis the lay before an l chill during delivery Stool we e p iti e for P e do mona The infant died 20 h urs later with cyano i dy pnea leukopenia and a mac lar ra h Culture of the infant blood ple n pleural exudate an l brain exudate were po itive for P udomona
Keefer and Hew tt[33] 1946	No clinical detail The pati nt died
Sol hi an l Khairat[03] 1948	A 28 year ol l pati t al t d in tl e 3r l month f ge tati n after a day fe C lt of th 11 l

TABLE 5—C ntinu d

	urine stool an l cervix we e po iti e f r l udo mona She d ed 33 days later I o tm rtem culture from the pericar lial flu l and lun w re positive for Pseudo onas an l *F coli*
H ll 1949	A 28 year ll pri nip ra was in luc d in th th month of pregnancy becau e f p e-eclamptic tox emia. She wa del ve ed f a stillborn femal and a male who d e l i 24 hours. Pseudon nas wa culture l from th patient s l loo l u n and c rvix and he d e l after 4 month illn with P eudo mona sep ticemia
N ra and Sann 19 2	A 29 y ar old primipar had diarrhe f r l m nth p r t abortion at 5 month ge tation Sh d l n th 3 th ho pit l lay ha ng had e th m all o er her bo ly l e l m na wa c ltured f m the loch a, amn ti flu l kin le on m uth ul ra tion, pleu al flu l na al exu lat an l f The infant appeared n rmal but d d 2 h ur aft r l rth with nten ely onge ted l r nd pleen Ps u l monas was r o ered f om the infant li e pleen b ne marrow nd meconium.
Hoffm n 19 1	A male twin infant wa demato ly pn i and cyan tic an l d ed d y afte b rth I eu lomona was cultu ed fr m th pleural u late Th i fant also had men n ti an l myocard ti Th moth e wa well
Korte 19	The mother ha l n ph ti after the 6th month of pregnancy A full t rm m l i fa t died o th 4th day with dy pn cyan i an l kin macule I seu l m na wa ultur d fr m th infant m l ll ear l r g ll bla ld r nd pleu a
Sto gh a l Sh n r 19.6	*2 cases* A 38 year ld n ult pa a ha l chill nd f e fo 2 day a d aborte l a 3 i ch f tu Her blood culture wa po tiv f r I eudomona but h impro e l and eco e l The fetu wa t infe ted A 22 y ar old mult gra ida w d li l of t ll born mal at 36 w k ge tat She h l l ck ach nau e omit ng hill n l fev r He l lood an l st l were p it f Pseu l m nas wh h was also gr wn f om the l l d lu s and pl en of the nf nt

TABLE 5—*Continued*

Walthard [435] 1904	A 35 year old multipara with chill and fever 3 days po tpartum P eudomonas was cultured from the lochia along with other organi m The patient re covered
Rolly [363] 1906	Following a septic and incomplete abortion P eudo monas was cultured from the patient s blood an l pinal fluid She died on the 11th day P eudomonas wa cultured from the heart valve and mo t of the body or_ans
Delmotte [9] 1910	An 18 year old primipara wa fel rile 2 days after spontaneous delivery P eudomonas wa cultured from th lochia but blood cultures were ne-ati e The patient reco ered
Soifer 1928	A 34 year old multipara with pain fever and chill follcwing incomplete eptic abortion was in luce l and the product of a 2 month ge tation recovered P eudomona was culture l from the blood an l placenta She reco ered
Gaucheraud and Figeaud [1] 1928	The mother had eptic endometriti at delivery but recovered in 10 days 4 day after delivery the in fant developed menin-iti and hydrocej halus P eu domonas wa cultured from the ventricular a pirate and the infant died on the 37th day (? contaminate l spinal tap)
Allin [4] 1941	A 27 year ol l patient ha l f er omitin- an l diarrhea durin_ deli ery of a premature infant (34 week) P eudomona was culture l from the moth er s stool She recovered and wa di charg l aft r a 1 month illnes On the 5th day the infant le elope l re l macular areas over the l ody and died with Pseudom nas menin- ti
Krau and Hunter 1941	*The j atient l a l enteriti th dav before an l chill* durin- deli ery Stools were po iti e fo I e do monas The infant l ed 20 hour later with cyano i dy j nea leukoj e ia and a ma ular ra h Culture f tl e infant s l lood j leen pleural xu late an l l rain exu late were po ti e for P u lomona
Keefer and Hewitt [33] 1946	No clinical details The pati nt d ed
Sol hi an l Kha rat [3 6] 1948	A ?8 ye r ol l j t nt al orte l in tl 3rd n o th of ge tat n fter a 2 l y f e C lt res of tl e l loo l

TABLE 6—4 Chronologic Listing of Reported Cases of Pseudomonas Infection of the Bones or Joints

Author	Age and Sex	Lesion	Treatment	Result	Remarks
Pawlowsky[338] 1889					Pseudomonas isolated from tuberculous joint
S h rm yer[881] 1895					Pseudomonas obtained from a prepatellar bursitis in pure culture
Perkins[340] 1901	35M	Acute purulent arthritis left elbow and abscess left 7th rib	Resection of rib and drainage	Died	No autopsy or blood culture
Wassermann[38] 1901		Arthritis knee	Amputation		
W t 1908	0F	Knee joint and leg bon	Mid thigh amputation	Recovered	Origin of infection unknown Pseudomonas from knee joint
Groves[18] 1909	8M	Secondary hip infection (after TBc) ? arthritis thumb	Autogenous vaccine	Rapid recovery	Only the hip was cultured Pseudomonas isolated
Pi elli[344] 192[illegible]	8 mo	Shoulder joint	Aspiration and vaccine	Rapid recovery	Pseudomonas isolated from joint aspirate
M l na 1930	10F	Right hip	Aspiration and vaccine	No change in 6 weeks	Pseudomonas isolated from hip

TABLE 5—*Continued*

Kohn [4] 1957	A 42 year old gravida V aborted 3 weeks after an upper respiratory infection The placenta was yellow and necrotic The 7 month fetus had numerous liver and other organ abscesses culturing Monilia and Pseudomonas The fetal blood was positive for Pseudomonas There was acute phlebitis of the portal veins and adrenal hemorrhage The mother recovered
Pennisi et al [3 9a] 1958	A 27 year old para ii gravida ii aborted a macerated infant about ten weeks before term following a traumatic douche The vaginal discharge was greenish yellow and foul smelling Blood cultures following antibiotic treatment were negative but Pseudomonas was grown from the patient s urine lochia and from the fetal lung tissue The mother recovered
Meyer [3 8] 1960	A 25 year old female was hospitalized for elective cesarian section 1 week prior to term She was catheterized and sectioned under spinal anesthesia giving birth to a viable male infant Several days later she became febrile toxic hypotensive went into pulmonary edema and died with ventricular fibrillation Antemortem cultures of blood and urine were positive for Pseudomonas Autopsy showed unilateral renal papillary necrosis with suppurative pyelonephritis and obstructing calculus in the left ureter

The portal of entry in many cases has been the birth canal Several of these lack complete documentation However it is apparent that systemic infection with *Ps aeruginosa* constitutes a serious threat to the pregnant woman and her fetus

OSTEOMYELITIS AND ARTHRITIS

Reports of arthritis and osteomyelitis due to *Ps aeruginosa* are uncommon Involvement of bones and joints in most cases can be attributed to hematogenous dissemination *Stanley*[404] *in 1947 col* lected 10 cases from the literature Additional reported cases are summarized with the previously reported cases in TABLE 6 Not in

TABLE 6—Continued

Author	Age and Sex	Lesion	Treatment	Result	Remarks
Herrell and Ni[illegible] 1945		Osteomyelitis	Streptomycin	Failure	No information
Kirz[8] 1947		Osteitis pubis			Following suprapubic operation on bladder
Fl[illegible]ey et al[1] 1947		Sequestra from contaminated fracture	A[illegible]	Recovered	53 air-borne battle casualties with 63 lacerated wounds—mainly open fracture of tibia—P[illegible] found in 18 sequestra (12 in pure culture)
Re[illegible]hmann et al 1949	7M	Osteomyelitis [illegible]	Streptomycin	Recovered	Organism encapsulated
C[illegible]rnevale and W[illegible]man[61] 1950	58M	Pyoarthrosis knee	Streptomycin locally and parenterally	Recovered	Followed abdomino-perineal—infection with [illegible] grown from knee
Glanz [illegible][4] 1950	3 mo M	Arthritis of the knee and left shoulder, sternum	Local injection streptomycin	Recovered	Metastatic purulent arthritis [illegible] peritonitis. P[illegible] in pure culture from joint aspiration
Friedenberg[illegible] 1950	64M	Osteitis pubis and destructive arthritis left hip	Extra-articular graft for fusion	Recovered	O[illegible] after suprapubic prostatectomy—Urine [illegible] culture [illegible]

TABLE 6—Continued

Author	Age and Sex	Lesion	Treatment	Result	Remarks
Bishop 1938	3? M	Right ankle joint and tibia	Incision and drainage	Rapid recovery	Burn of extremity followed by subcutaneous abscesses. Pseudomonas in joint pus
	15 mo later	Right ankle	Incision and drainage, autogenous vaccine	Healed in 2 weeks	
Ku on ki 1938	1?M	Osteomyelitis spine D9 10 11	No data	No data	Daily catheterization for stricture followed by pyelonephritis and psoas abscess—Pseudomonas in abscess and in urine
Bormuth 1939		Acute osteomyelitis of sternal manubrium	Sequestrum removed (Pseudomonas grown)	Rapid recovery	? from septic spread of furuncle on right arm—not cultured)
Schein 1940	56M	Osteomyelitis spine (D7 8) ? abscess mediastinum	Sulfa	Slow recovery	Had bacteremia after cystoscopy for renal lithiasis. Urine and blood positive for Pseudomonas
Fisk 1942	7?M	Chronic arthritis	Oral vaccine	No relapse for 3 years	Had gastrointestinal Pseudomonas but no evidence of suppurative arthritis
Burdick 1945	60M	Abscess costal cartilage	Radical excision	Recovered	Pseudomonas bacteremia after urinary catheterization—Lesion appeared after suprapubic cystotomy

TABLE 6—*Co tinue l*

Author	*Age and Sex*	*Lesion*	*Treatme t*	*Result*	*Remarks*
K eple [s] 1954	9 mo M	*O teomyelitis of* spine			
Le gh et al [9] 1955	63M	O teomy l tis of sp ne L1 2 D7 8	Ant biotics	Re red lowly	Following operation for renal cal culus—P eu l mona a pirated from bone le on
He on and Co e try [9] 1956	50M	TI1 12 and L1 2 and adjacent cort e	Immob lization with ca t Cor tiso e and x ray	*Sol d bony* fu ion in 6 mo ths	*Cy to c y for* uretero lithia s 7 months previou ly Pus from L grew P eudomo as
Wat bren [430] 1957	2 wk F	O teomyel tis right humer	St eptomycin oxytetracycline g mma gl bul		Exchange tra fu ion f r erythro bla to i f tal 2 we ks later *o teomyel ti devel d* Reco ered

TABLE 6—*Continued*

Author	*Age and Sex*	*Lesion*	*Treatment*	*Result*	*Remarks*
Coleman and Lowry[77] 19[illegible]1	Premature infant	Purulent arthritis knee	Streptomycin	Recovered	? Source umbilical cord or oral thrush (Pseudomonas isolated)
Walker[433] 1952	7 mo M	Osteomyelitis tibia bilateral	Polymyxin B i m incision drainage curettage	Recovered	Followed marrow infusion (Pseudomonas isolated)
Jawetz[illegible] 19[illegible]2	2½	Purulent arthritis	Polymyxin B locally	Recovered	No details
		Osteomyelitis roof left orbit	Polymyxin B intrathecal	Recovered	Had Pseudomonas meningitis secondary to skull fracture and burr hole
Yow[illegible] 1952		No details			
Kreitner[illegible] 19[illegible]	53M	Osteomyelitis sacrum	Blood transfusion and antibiotics	Recovered	Had operation for cancer of rectum—developed abscess in sacral wound cavity
Manoukian[94] 1953	60M	Osteitis pubis—purulent with sequestrum	Polymyxin B local and intramuscular incision and drainage	Recovered	Occurred 1 month after suprapubic prostatectomy (Pseudomonas isolated)

TABLE 6—Co n u d

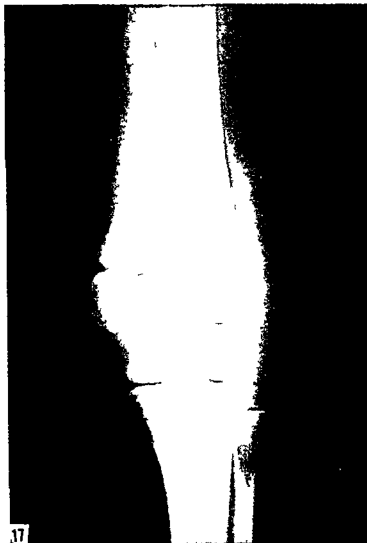
At thor	Age a d Sex	Le on	Treatm e t	Res lt	Remarks
Krefler [5] 1954	9 r o M	O teon yel tis of p ne			
Le gh et al [9] 1955	63M	O teo yelit of spine L1 2 D7 8	Ant bi tic	Reco ered slowly	Foll wing operation for renal cal culus—I eudomona aspirated from bon le ion
Hen on and Co entry [6] 1956	50M	T11 12 and L1 a d adjace t c rt ce	Immobil at o w th ca t C r ti one and x ray	Sol d l ony fu ion in 6 months	Cy to copy for uret ro lithia is 7 months p e ou ly Pus from L grew P eudomonas
Wa bren [450] 1957	2 wk F	O teon yelitis right humeru	Streptomycin oxytetracycl ne gamma glol ulin		E change tran fu ion f r rytho bla to fetali 2 week lat r o teo yel tis l veloped Reco ered



FIG 16—*Ps aeruginosa* arthritis Aspiration from the swollen left knee was productive of a thin non sanguinous pus from which *Ps aeruginosa* was obtained several times on culture

cluded in the listed cases are suppurative processes in the region of the mastoid often associated with otitis media due to *Ps aeruginosa* Occasional cases [33] are not tabulated because of insufficient data Pseudomonas infections of bones and joints are frequently preceded by urinary infections

Lame [60-6] who considers osteitis pubis to be an osteomyelitis has postulated a series of lesions involving bones and joints which may result from dissemination of infections of the urinary tract This sequence involves consecutively osteitis pubis purulent infection of the hip joint and vertebral osteomyelitis He found in the literature three patients reported to have osteitis pubis who subsequently developed arthritis of one or both hips [131 6 3 9] Only one of the lesions was cultured and *Ps aeruginosa* was recovered both from the hip and from the urine All 3 cases and a fourth presented by the author occurred following prostatectomy



Fi 17—An X ay film of the d tal femu of the patient illu tr ted i Fi 16 L g o teolytic d fect in l ng the epiphy i a d cortex are pp e t

Listed in TABLE 6 are several reported cases of spinal and pelvic osteomyelitis due to *Ps aeruginosa* which followed operative procedures on the urinary tract Since it is usual for roentgenographic demonstration of such lesions to lag weeks or months behind symptomatic onset specific identification of the causal agent in many cases depends on aspiration smear and culture of the osseus lesion itself



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FIG 18—Pseudomonas colonies synovial surface right hip causing acute arthritis Hematoxylin eosin (× 380)

It has been pointed out by Leigh et al [69] that in such cases the entire spinal column should be examined for multiple lesions

We have followed the clinical courses of 3 patients with infections of joints due to *Ps aeruginosa* One of them a 5 year old male with acute lymphocytic leukemia insidiously developed a painful swollen left knee with associated high fever (see FIGURE 16) The initial aspirated material contained many polymorphonuclear cells but was sterile All subsequent aspirations were positive for *Ps aeruginosa* No septicemia could be demonstrated The situation

sugge ted bacterial contamination at the time of the initial pro cedure However a large o teolytic defect in the adjacent di tal femur with epiphy eal involvement and cortical de truction which originally was considered to be an atypical leukemic lesion proved on biopsy and culture to be osteomyelitis due to *Ps aeruginosa* (ee FIGURE 17) Attempts at con ervative therapy including local irri gation with polymyxin B together with sy temic antibacterial ther apy were unsuccessful Sub equent inci ion and drainage of the knee joint with curetting of the o teolytic lesion and immobiliza tion of the joint resulted in negative cultures and a low but definite clinical improvement

FIGURE 18 illustrates colonies of *Ps aeruginosa* on the synovium of the right hip joint of a patient with chronic leukemia who had acute septic arthritis with p eudomonas epticemia

EYE

Since 1885 when infection of the eye due to *Ps aeruginosa* was fir t reported in the form of dacrocystitis de tructive le ions in var ious forms cau ed by this organi m have been de cribed Spencer s article on *Ps aeruginosa* infections of the eye includes an extensive list of references on this topic[40] The mo t common form of eye infection is corneal ulcer which may pread with alarming rapidity to become panophthalmitis The first recognized ca e was reported by Sattler[319] in 1891 A typical history is that of minor abrasion or foreign body followed in one to three days by the appearance and rapid growth of a white ulcer with a characteri tic area of necro is and a emitran parent center The bacteria migrate rapidly from the corneal tissue into lymph paces[41] The organi ms multiply rapidly at the point of entry extend into the normal cornea and cause widespread destruction as they form endotoxins and exotoxins[93]

[93] Such infections are notoriou ly resi tant to therapy and are recognized to be among the most erious corneal lesions [3 361] Prior to the advent of sulfonamides lo s of vision with or without enuclea tion was the common result Infection may al o take the form of con junctivitis[101] necrosis of the eyelids[144 147] dacrocystitis[410] punctate

keratitis meibomitis and endophthalmitis Contaminated medicinal solutions have been implicated in some case [1, 7, 414, 446]

Fisher and Allen[134] have recently investigated the role of pro tease in ocular damage due to *Ps aeruginosa* They have noted a correlation between the proteolytic capacity of the strain and the degree of corneal ulceration Severe corneal damage was produced in animals utilizing a cell free preparation containing a protease or possibly more specifically a collagenase Further immunologic studies by these authors[134b] suggested to them that antibodies may be produced against these enzymes with interesting therapeutic implications

EAR

Prior to 1940 the principal organi ms cultured from *otitis ex terna* lesions were fungi of one type or another Since then it has been shown that gram negative bacteria specifically *Ps aeruginosa*



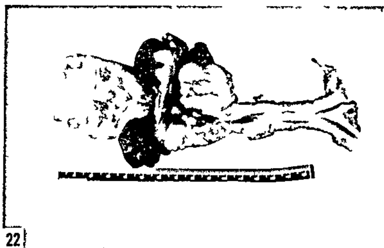
Fig 19—Otiti m lia d e to *Ps aeruginosa*

20



Fı 20—(al o e) Int r tıt al I u l r na olom tl y oı l gland H m t xyl n (× 2(0)

Fıc ?1—(b low) l e l m lyn ı l ad nıtı Hen t xylın e sın (× 75)



23

Fig 22—*(above)* Necroti ing hemorrhagic ton ll t lue to *Ps a ruginosa*

Fig 23—*(b low)* F cal n cr due to I eudomonas va culiti fa cial ton il Hematoxylin eo in (× 12)

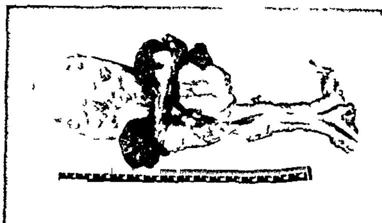
are frequently pre ent I ersi tent infection may develop partic ularly in moi t tropical climate [1 1 1 t r 4 8] Complication uch as ab ce s of the brain [373] ma toiditis and thrombophlebiti of the lateral sinus occasionally occur and several ca es have been asso ciated with meningitis either by direct exten ion or by way of the blood tream [7 109 144 147 11 7 18 3)]

One of our patients developed otitis media due to *Ps aeruginosa* The histologic picture may be een in FIGURE 19 It is not known whether this was a primary or secondary infection for the patient died with dis eminated lesions

MISCELLANEOUS INFECTIONS

Some of the more frequent and more prominent sites of infection due to *Ps aeruginosa* have been discussed in detail However many other region of the body may be involved Some of these include Ischiorectal ab ces e [) 109 119 144 147 41 5] absces es of the liver [7 43 447] subhepatic [33] and subphrenic ab ce es [3] ab ces es of the thyroid gland [457] gastrointestinal ulcerations [4] abscess of the brain [7 340 373] gallbladder [0] cholangitis [38] pelvic abscess [33] e oph agitis [15] abscess of the parotid gland [63] dental caries [,] pericarditis [1 68 1 0] peritoniti [1 13 0 64 6 34)] multiple metastatic abscesses [36 340] arteriovenous fistula [87] and pulmonary arteritis [173]

Additional infections in our own eries either primary or second ary are illu trated by photographed micro copic ections of the thyroid gland (FIGURE 20) lymph node (FIGURE 21) and ton il (FIGURES 22 and 23) on the preceding two pages



23

FIG 22—*(above)* Necroti in hemorrha ic ton illiti due to *Ps a rugi a*

FIG 23—*(below)* F al n cro s due to P eu lomonas va culiti faucial ton il Hematoxylin-eo in (× 1?)

of references dealing with data on toxicity resistance antibiotic synergism and in vitro testing is available in Jawetz monograph

SYSTEMIC INFECTION

Bacteremia or endocarditis due to *Ps aeruginosa* should be treated immediately with polymyxin B which is probably the drug of choice [10, 6, 40, 461] In the presence of good renal function prolonged therapy with polymyxin B in full dosage is probably safe [10] Recommended doses are 1.5 to 2.5 mg/Kg/day in 3 or 4 equal intramuscular injections for two weeks with a daily maximum of 200 mg Polymyxin B has been given both intramuscularly and intravenously for extended periods in at least one case of endocarditis without evidence of permanent toxicity In the presence of pre existing renal disease a maximum dosage of 1.0 to 1.5 mg/Kg/day with careful clinical and laboratory supervision is indicated One per cent procaine solution may be added to minimize local irritative effects Oxytetracycline may act synergistically with polymyxin and probably should be administered concurrently in oral doses of 250 mg 4 times daily Sensitivity studies should be performed in all cases although this should not delay the institution of appropriate treatment Neomycin may prove valuable in some cases Polymyxin has been given intravenously (200 mg in 2000 ml of fluid) but this route of administration needs further evaluation

URINARY INFECTIONS

Polymyxin is probably the drug of choice in acute and chronic urinary tract infections due to *Ps aeruginosa* [10, 6, 407, 461] This should be given intramuscularly in full doses possibly in conjunction with oxytetracycline Local urethral or bladder instillation of polymyxin solutions may be useful in some cases

INTRATHECAL ADMINISTRATION

Since *polymyxin does not cross the blood brain barrier* [44] the route of choice for pseudomonas meningitis is intrathecal Jawetz

3 *Antibiotic Therapy*

Several excellent sources of information about the treatment of infections due to *Ps. aeruginosa* with polymyxin B are available [6, 430, 44, 461] Much of the following data can be found in a monograph by Jawetz [6] and in an article by Waisbren [431]

The polymyxins, originally reported in 1947 [1, 404b] are basic polypeptides with a relatively narrow antibacterial spectrum Their action is predominantly against gram negative organisms and is bactericidal Most strains of pseudomonas are inhibited in vitro by a concentration of polymyxin B of 2.0 micrograms per milliliter or less [6] Development of resistance is uncommon in originally susceptible strains cross resistance with other antibiotics has not been encountered Detailed studies on the action of polymyxin against *Ps. aeruginosa* are available [3]

Absorption by the oral route is insignificant but usefulness as the sole agent for preoperative sterilization of the bowel is limited by its narrow spectrum of activity No significant blood or urine levels are obtained after topical application [1] By the intramuscular route the drug is well absorbed and distributed reaching an effective level in the blood in one half hour and a peak in two hours The optimum bactericidal effect of polymyxin B is obtained when sufficient concentrations of the drug are brought into direct contact with the source of actively multiplying organism Since transfer of polymyxin from the bloodstream into body cavities is often impaired it becomes essential to select the appropriate route of drug administration for maximum therapeutic effect

Dosage and duration of treatment is also of great importance since neurotoxic and nephrotoxic effects have been reported These appear to be transient within the recommended dosage schedule but in the presence of renal disease with elevated non protein nitrogen serum levels may accumulate necessitating careful clinical and laboratory supervision of therapy After parenteral administration polymyxin is largely excreted in the urine A fairly complete list

this time [c] Intrapleural administration of polymyxin for the treatment of empyema may be of value with or without the use of enzymatic agents Irrigation of infected wounds sinuses or joints with solutions of 1 to 10 mg polymyxin B per ml sterile saline has been of therapeutic value when combined with adequate drainage or enzymatic debridement

THERAPY WITH COLISTIN SALTS

Recent reports in the American literature [179, 206, 300, 364, 391, 406] indicate that a new antibiotic colistin produced by *Aerobacillus colistinus* may prove useful in the treatment of pseudomonas infections Colistin was first reported in 1950 by Koyama and his associates [49] The two commercially available forms* are colistin sulfate (Coly Mycin S) the oral form and sodium colistin methane sulfonate (Coly Mycin M) an intramuscular preparation Much of the investigation to date has been carried out in Japan and Italy A good bibliography is listed by Schwartz et al [391] These polypeptide compounds appear to have a similar spectrum and activity to that of polymyxin B however probably without serious nephrotoxic features Preliminary studies indicate that for *Ps aeruginosa* these new drugs are rapidly bactericidal sensitive strains do not readily develop resistance and there is no cross resistance with the broad spectrum antibiotics

Graber et al [1 9] found *Ps aeruginosa* to be highly sensitive to colistin sulfate only 5 of 18 strains requiring a plasma level as much as 3 12 μg /ml for bactericidal activity They recommend its use in pseudomonas septicemia complicating severe burns McCabe et al [300] found colistin valuable in the treatment of wound infections due to *Ps aeruginosa* Lack of nephrotoxicity was confirmed but the effect against pseudomonas was less uniform than that of polymyxin B

Gastrointestinal absorption of colistin is negligible except possibly in small infants Ross et al [364] suggest that for the pediatric age

* These trade names in parentheses are the property of Warner Chilcott Laboratories

recommends the use of 5 mg of the sterile powder dissolved in 10 ml of saline to give a final concentration of 0 5 mg per ml. This is injected daily for 3 days, then every other day for a total of 10 to 15 injections.[6a] Procaine must not be added. The total daily dosage must not exceed 5 to 10 mg for adults or 2 mg for small children. Treatment should continue for at least two or three weeks after obtaining negative spinal fluid culture. The additional use of intramuscular polymyxin 50 mg 4 times daily has been suggested by some authorities.[430] Neomycin and Streptokinase-Streptodornase has been used successfully in some cases.[103, 4] Experimental reports of the effects of intracisternal injection of polymyxin are available.[40, 3b]

ORAL ADMINISTRATION

Tablets containing 50 mg of polymyxin B are available for oral administration. The daily adult dosage is 400 to 600 mg in divided doses.[4] For small children 15 to 20 mg/Kg/day for 10 days is suggested for the treatment of diarrhea caused by *Ps. aeruginosa*. Descriptions of clinical cases are available.[310, 370, 433, 44] A suggested dose for the treatment of carriers has been 0 5 gm four times daily.[436a]

TOPICAL ADMINISTRATION

Polymyxin has found wide use in the treatment of burns, infected *ulcers* and large wounds.[1, 46, 436] A concentration of 0 5 to 1 0 mg per ml, either alone or with neomycin or bacitracin, has been useful in preventing secondary infections. No significant blood or *urine levels are* obtained after topical application to large burns.[1] Similar concentrations have been used with success for the topical treatment of otitis externa due to *Ps. aeruginosa*.[386] Polymyxin is urgently *indicated* for the treatment of corneal ulcer. 20 to 25 mg/day subconjunctivally has been recommended.[110, 183, 317, 364, 440]

MISCELLANEOUS INFECTIONS

Treatment of infections of the respiratory tract with aerosol has been reported,[6] but cannot receive unqualified recommendation at

4 *Pathology*

The characteristic pathologic lesion of *Ps aeruginosa* infection is a diffuse acute vasculitis in which the walls of small arteries and veins are extensively invaded by pseudomonas organisms (FIGURES 2 3) This process is associated with extravascular hemorrhage and intravascular thrombosis There is bland hemorrhagic necrosis of the surrounding tissue Such lesions were extensively described by Fraenkel[144-147] and subsequent reports have served to elaborate and confirm his observation[14] Areas supplied by these infected vessels become necrotic and typically assume the appearance of hemorrhagic gangrenous ulcer The close relationship of bacteria to blood vessels apparently favors dissemination of infection Secondary lesions are usually hemorrhagic and necrotic and are almost always non suppurative

The pathologic lesions of pseudomonas may be found at any or all of the various portals of entry of infectious agents into the body The e include the mouth pharynx middle ears larynx lungs esophagus stomach intestines genitourinary tract and skin In some cases the organism may be introduced into the spinal canal by needle or into the bladder by catheter or into the central nervous system by penetrating injury Cellulitis in our own experience has followed the aspiration by needle of bone marrow at the iliac crest

In 22 subjects autopsied at the Clinical Center during the period of 1954 to 1957 histopathologic lesions of *Ps aeruginosa* were found with the following frequency skin and subcutaneous tissues 10 lungs 9 oral mucous membranes and intestine 5 each kidney esophagus and myocardium 3 each spleen liver pancreas thyroid gland and paranasal sinuses 2 each and pericardium hip joint pleura middle ear and conjunctiva single instances By contrast the distribution of post mortem cultures in the same subjects was heart blood 13 (2 other patients had sterile cultures and 7 were not cultured) lung 8 spinal fluid 5 subcutaneous tissue and pericard

group an oral dose of 15 mg /Kg daily in an eight hour dosage schedule would be ample Gua ardo[184] has reported powerful activity of colistin against gram negative bacteria in the intestinal flora He found that infantile diarrhea responded well This has also been the experience of others [66]

Clearly these compounds show promise in the treatment of infections caused by *Ps aeruginosa* and deserve further evaluation

At this time it is difficult to assess in any specific way what the anticipated results of a given therapeutic regimen should be Large series of patients treated comparably are not available for analysis in most types of infection due to *Ps aeruginosa* However it does seem clear that systemic or meningeal infection is always serious and carries a poor prognosis particularly in the absence of adequate natural body defense mechanisms Local infections on the other hand frequently respond favorably when recognized early and treated appropriately

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5 *Summary*

A review of infections caused by *Ps aeruginosa* has been presented. What general principles can be derived from this collected information and how can they be specifically applied? Which areas of investigation will be most rewarding in terms of increased knowledge of the organism and better clinical management of the patient?

First of all there must be general recognition that *Ps aeruginosa* is potentially pathogenic for man. Infection is most likely to occur in a setting where body defense mechanism are immature, as in infants, or overtaxed as in patients already debilitated from some other cause. Therapeutic measures designed to combat one condition may provide an environment favorable for the establishment of resistant pseudomonas infections. Examples of this are numerous and include prolonged administration of antibiotics, the use of ionizing radiation and chemotherapeutic agents in neoplastic disease and in kidney transplantation, the employment of venous and urinary catheters, the use of pump oxygenators for extracorporeal circulation in cardiac surgery, and the use of lumbar puncture for diagnostic or therapeutic reasons. These procedures are often useful and necessary but have introduced problems which must be anticipated, recognized and treated effectively.

Ps aeruginosa is ubiquitous and may thrive in the usual antiseptic solutions used for preparing skin, storing catheters and other surgical instruments [10 3 6 31 3 6 4 4]. The antibacterial activity of such solutions may diminish over a period of time to encourage this growth [6 ?]. Bed pans and urine bottles are the most likely sources for contamination of the hands of ward personnel [30]. In this regard carbolic acid as a 2 per cent solution has been reported to be an effective antiseptic.

With the possible exception of direct introduction of organisms into the blood or spinal fluid, serious infection with pseudomonas would appear to be uncommon in non debilitated adults. It is the susceptible patient for whom strict precautionary measures must be

ial fluid 3 each ascitic fluid synovial fluid and intestine 2 each and oral mucous membrane pleural fluid kidney spleen liver middle ear paranasal sinuses eye nose and lip single instance The considerable differences between the histopathologic and bacteriologic distribution are attributable to differences in sampling

The significance of a post mortem culture of pseudomonas is much greater than is the significance of bacterial contaminant such as *E coli* Fraenkel found only 75 instances of positive pseudomonas cultures among 6646 positive blood cultures in 11 286 autopsies Since pseudomonas usually outgrows other bacteria in contaminated material and is so infrequently present in post mortem culture positive autopsy cultures of this organism are highly significant and should serve to alert the pathologist to search the tissues carefully for evidence of invasion In 1922[147] Fraenkel remarked that scarcely an organ in the body had not been at one time or another described as the site of pseudomonas infection

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taken These should include isolation from known sources of infection and frequent changes of antiseptic solutions or other possible bacterial reservoirs The more susceptible the patient as judged clinically the more stringent should be the precautions Antibiotics particularly broad spectrum drugs should be withheld in the absence of specific indications Prolonged and prophylactic treatment with antibiotic agents is to be discouraged Strict attention to bed sores particularly those near the ano genital area is important since these may offer a convenient portal of entry to the blood stream The presence of oral moniliasis may indicate the existence of an environment favorable to pseudomonas since the e organisms frequently occur together The appearance of characteristic cutaneous lesions or less specific signs such as fever jaundice unexplained neurologic symptoms or sudden shock may herald the onset of septicemia Other clinical features of infection have been discussed Cultures should be taken from suspicious areas and sensitivities performed

Major problems in the management of pseudomonas infection have been (1) the apparent inability of the host to summon adequate natural body defenses and (2) the resistance of the organisms to available therapeutic agents Polymyxin B and neomycin or possibly colistin appear to be drugs of choice in most cases The early institution of appropriate therapy for a sufficient period of time is vital since pseudomonas infections tend to assume a chronic and relapsing course

Several areas require further investigation Rapid simple methods of bacteriologic identification are needed Studies on modes of transmission are suggestive but not conclusive The relation of cutaneous lesions to the Schwartzman phenomenon is of interest and not well understood [13] The mechanism of leukopenia and of shock has been studied but needs further clarification particularly with reference to the role of circulating endotoxin The role of adrenal cortical steroids as a possible predisposing factor is of interest and difficult to evaluate The use of these compounds in the treatment of bacteremic shock due to *Ps aeruginosa* has not been successful in our hands [140] The status of gamma globulin needs

investigation In our own experience in patients with leukemia serum levels of gamma globulin did not change significantly with the onset of pseudomonas infection Rosenthal et al[363] rendered mice susceptible to pseudomonas infections by pretreatment with cortisone and were able to protect these animals by administration of human gamma globulin A synergistic effect was obtained by the combination of oxytetracycline with gamma globulin or plasma[3] Other studies on the potentiating effects of gamma globulin are available[134, 193, 44] The role of phagocytic action on pseudomonas infection in mice is being studied[3 3] Investigations of the properdin system may be useful in our understanding of natural body defenses[343] Possibly the best attack would be the most direct namely the discovery of an antibiotic agent specific in its action against these organisms and without deleterious side effects The colistin salts or related compounds may provide this need Meanwhile the intelligent application of already established principles should prevent or abort many of these resistant infections due to *Ps aeruginosa*

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